EBRAINS Human Brain Project Co-funded by the European Union POLITÉCNICA

UPM INNOVATION TEAM
PRESENTS

WHERE IS EUROPEAN BRAIN-INNOVATION HAPPENING?

THE ROLE OF TECH-BASED START-UPS

AUTHORS:
GUILLERMO VELASCO, TERIS DURÁN, BLANCA BELTRÁN, GONZALO LEÓN

CONTRIBUTORS:
ROMAN KIREEV, BULUT DURMAZ, ALEJANDRO FERNÁNDEZ, EDUARDO SÁNCHEZ

´Where is European Brain Innovation Happening? The role of tech-based start-ups´

Universidad Politécnica de Madrid. HBP Innovation Team

Nov 2021

Version (V.1)

UPM-2021-03

Project Number:	945539	Project Title:	HBP SGA3

Document Title:	**´Where is European Brain Innovation Happening? The role of tech-based start-ups´**
Document File Name:	report_start_ups_finalversion1.docx
WP(s)/Task(s):	WP8 T8.6
Project Objective(s):	Industrial engagement
WP Objective(s):	Industrial engagement
Output(s):	Report
Dissemination Level:	PU = Public
Delivery Date:	SGA3 M20/ 08 11 2021
Author(s):	Guillermo Velasco (UPM), Teris Durán (UPM), Blanca Beltrán, Gonzalo León (UPM)
Compiled by:	Guillermo Velasco (UPM)
Contributor(s):	Roman Kireev (UPM), Bulut Durmaz (UPM), Alejandro Sánchez (UPM), Eduardo Sánchez (UPM)
Abstract:	The HBP Innovation team is mobilising brain-technology start-ups around the services offered by EBRAINS. The initiative implies the organization of a series of Solution Workshops where selected European start-ups and HBP leader scientists present their projects, discuss, and interact. To support this initiative with empirical evidence and understand the contextual circumstances of the start-ups operating in Europe, the UPM has elaborated the present document. It concisely presents the results of an intense searching, mapping, and classification process of start-ups actively working in different areas of the brain-technology domain. The insights and conclusions contained in the report do not only serve as background material for the workshops but can also be seen as a tool of business-intelligence that will support future EBRAINS engagement decisions and strategic plans.
Keywords:	Innovation, start-up, brain research, brain technology, entrepreneurship
Target Users/Readers:	Innovators, innovation managers, neuroscience researchers, neurocomputing researchers, technology developers, policy makers

ACKNOWLEDGMENTS

We are very grateful to the EBRAINS members for their advice. We would also like to give thanks to the start-ups and HBP scientists that have participated in the pilot of the Solution workshop initiative.

This work has been funded by the European Commission under grant 945539 (HBP SGA3) of the "Human Brain Project" (HBP) and elaborated by the Innovation Team of the Universidad Politécnica de Madrid (UPM) within the task T.8.6 of HBP SGA3.

ABOUT THE AUTHORS

Guillermo Velasco is Scientific Manager at the UPM Innovation and Technology Transfer Node of the Human Brain Project (Universidad Politécnica de Madrid). He is also Honorary Senior Lecturer in The Manchester Institute of Innovation Research, within the Alliance Manchester Business School. He holds a PhD in Innovation & Foresight by The University of Manchester, and a MPhil in Innovation Economics and Management from the UPM. Guillermo has a Bachelor of Engineering in Organization and Industrial Economics and is certified associated expert on 'Design Thinking´ as application consultant. He has participated in numerous Foresight and innovation projects in the EC and other international bodies. He has published more than 30 articles and papers in these areas.

Teris Duran has a degree in International Trade, specialization in International Business, Magister in Economics and Business Management, and diplomas in the International and Financial Management area by the Universidad Metropolitana (Unimet) and the Universidad Autónoma de Madrid (UAM). She works as a researcher supporting the exploitation activities of the Innovation team of HBP-UPM. She has varied work experience in international trade, business, banking, finance, insurance, and customer service.

Blanca Beltrán is graduated in Business Administration and Law. After working in the corporative field, she decided to pursue her passion for human consciousness and how the brain system works within human beings. She is currently following a Master of Liberal Arts (ALM) field Psychology and collaborating with the UPM for the Human Brain Project.

Gonzalo León is Professor of Telematics Engineering at the Universidad Politécnica de Madrid (UPM). He is also Special Policy Advisor for International Relations of the Ministry of Science and Innovation, Madrid (Spain), Spanish Representative at the Strategic Forum of International Cooperation (SFIC) of the EU Council, Spanish Representative of the Dialogue 5+5 on Science, Innovation and Higher Education, and Vice President of the Foundation CIRCULO "Technologies for Defence and Security". He has been part of the Expert group for the Lisbon Strategy in R&D, the European Research Infrastructure Expert Group, the Space Research Advisory Group for FP7, and the Expert Group on synergies between framework programmes and structural fund.

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ABSTRACT

The Human Brain Project (HBP) is putting in place numerous actions to boost the utilisation of its developed tools by scientific institutions, hospitals, and industrial companies. Most of these users belong to Neuroscience, Neurocomputing and Neuro-medicine sectors and operate within very well-defined technology intensive markets.

In this context, an ongoing initiative led by the HBP Innovation team - taking place during the last years of the project (2021-2023) - aims to mobilise brain-technology start-ups and spin-offs around the services offered by EBRAINS[1], the HBP research infrastructure. An effective connection and involvement of these emerging companies to HBP should contribute to keep on building a critical mass of users that guarantees the sustainability of the RI beyond 2023. The initiative implies the organization of a series of Solution Workshops where selected European start-ups and HBP leader scientists present their projects, discuss, and interact. In fact, a dynamic dialogue with these companies is essential for HBP to gain visibility and demonstrate in a practical and straightforward manner, the full potential of the infrastructure.

To support this initiative with empirical evidence and understand the contextual circumstances of the start-ups operating in Europe, the UPM has elaborated the present analysis. The report concisely presents the results of an intense searching, mapping, and classification process of start-ups actively working in different areas of the brain-technology domain. The insights and conclusions contained in the report do not only serve as background material for the workshops, but also need to be seen as a product of business-intelligence that can support future EBRAINS engagement decisions and strategic plans.

1 https://ebrains.eu/

INTRODUCTION

Innovation in brain technologies is happening today with the participation of many types of actors, both public and private. Many large firms, SMEs, hospitals, universities and research centers have increased their role in moving ideas to the market and in accelerating their intake in clinical practice.

Within this context, the role of technology-based start-ups is increasing. Frequently, these companies exploit research results obtained in previous projects. In other cases, they depart from basic and applied research and manage to scale in their technology maturity processes. In any case, start-ups usually attract the interest of large firms and risk capital investors. This study is focused on this type of companies and the role they play in brain innovation.

Firmly aligned with the *Small and medium-sized enterprise (SME) strategy of the European Commission*[2], there are in fact several remarkable policy actions in Europe that try to stimulate entrepreneurship and facilitate the growing and consolidation of young businesses. In this respect, *Start-up Europe*[3] is an initiative that aims "*to connect high tech start-ups, scaleups, investors, accelerators, corporate networks, universities and the media*". It includes, on one side, a selection of EU funded projects and initiatives like the *EU Start-up Nation Standard*[4], with a focus on helping entrepreneurs to set up a company and expand it internationally. It promotes alliances and technology transferring from universities, while working to offer easier access to funding.

On other side, *Start-up Europe* also hosts the *Innovation Radar*[5], which is the EC data-driven instrument to locate high potential innovations emerging from EU-funded R&I projects. The objective is to make visible EU innovation outputs to investors, business, professional people, and the public. The *Digital Innovation and Scale-up Initiative*[6] (DISC), in addition, is a geographically oriented initiative that seeks to reduce the market gap between the central, eastern, and south-eastern Europe (CESEE) region and the innovators operating in other European regions. Besides, the *Start-up Europe Club*[7], is a webpage tool through which anyone involved and interested in the start-up environment can find relevant information and resources related to potential partnerships, investments, and eventual funding. These

2 https://digital-strategy.ec.europa.eu/en/news/sme-strategy-launched-european-commission

3 https://digital-strategy.ec.europa.eu/en/policies/start-up-europe

4 https://digital-strategy.ec.europa.eu/en/policies/start-up-europe

5 https://www.innoradar.eu/

6 https://digital-strategy.ec.europa.eu/en/news/launch-digital-innovation-and-scale-initiative-disc

7 https://start-upeuropeclub.eu/

initiatives may serve as an example of the efforts made by the European Commission to enlarge and strengthen the European SME and start-up ecosystem.

In parallel, the activity of the European Institute of Innovation and Technology (EIT)[8] is focused on the creation and consolidation of entrepreneurial skills, with special efforts in stablishing links between actors of the ´knowledge triangle´ (business, research and education) and installing in the European ecosystem right conditions for the effective functioning of the ´EIT Innovation Communities´[9]: EIT Climate-KIC, EIT Digital, EIT Food, EIT Health, EIT InnoEnergy, EIT Manufacturing, EIT Raw Materials, and EIT Urban Mobility. These communities cover different innovation needs like, among others, the identification of partners that facilitate the translation of technology solutions to the markets, the promotion of business collaboration ventures, or the attraction and generation of talent.

Finally, we necessarily have to highlight the mission of the European Innovation Council (EIC)[10] which, embedded in the new Horizon Europe programme, has a budget of €10.1 billion to "identify, develop and scale up breakthrough technologies and game changing innovations". The initiative provides funding to start-ups and SMEs, with attention to the different stages of the maturity scale. Funding modalities of the mission include direct equity, quasi-equity investments, and grants.

However, in a context where national and European authorities are demonstrating such a strong interest, it is quite surprising that there is not yet a clear consensus, neither in academic nor institutional literature, on what should be formally understood as a ´star-up´ organization. To address this gap and better assimilate what is analysed and commented in this report, preparing our audience for a fluent and reflective reading experience, we will refer below to some widely recognised characteristics of this type of organisation and recap some assumptions about their nature and raison d'être.

Start-ups, from a very general perspective, show a remarkable predisposition to innovation, with special interest on devising radical and disruptive solutions. The solutions provided by this type of companies normally have a strong technological dimension. Being the age of these small companies very often less than 10 years, they suffer from continuous transformation processes, being such transformations of organizational, economic, and/or strategic nature. In fact, and because of their youth and small size, these companies are subject to very quick changes, instabilities, and sometimes experience unexpected and exponential growths. However, managing decisions are usually taken rapidly and changes are adopted with high levels of flexibility.

8 https://eit.europa.eu/who-we-are/eit-glance

9 https://eit.europa.eu/our-communities/eit-innovation-communities

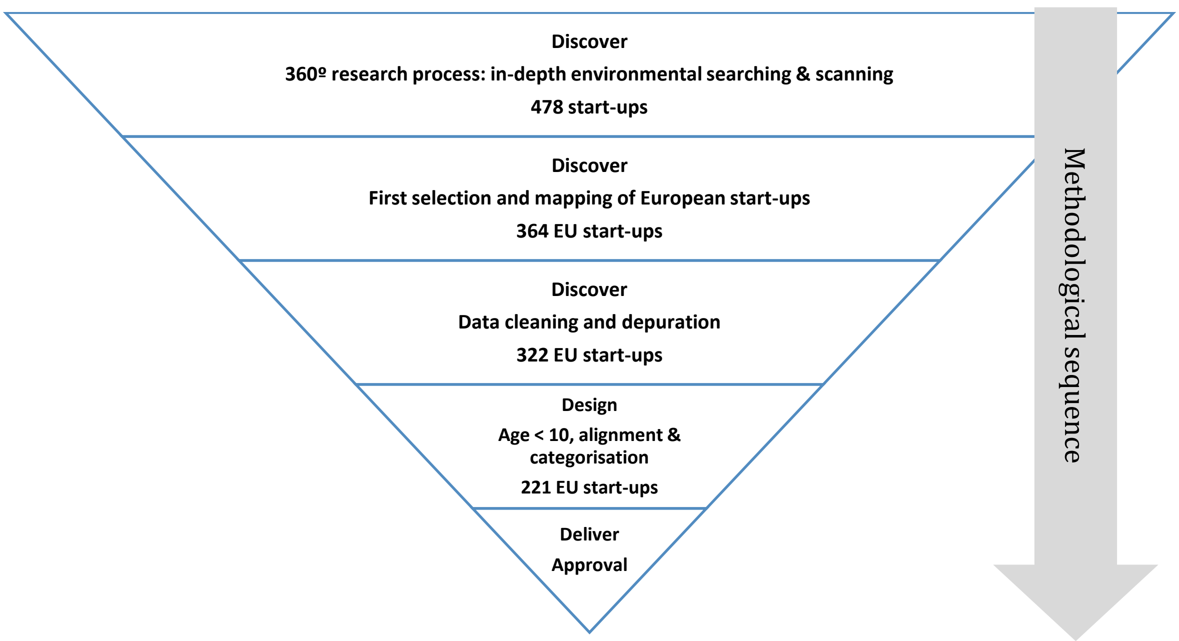
10 https://eic.ec.europa.eu/about-european-innovation-council_en

While presenting fragile structures and reduced staff, teams in these firms generally shows high levels of enthusiasm and a strong commitment with the project. Funders very often demonstrate great expertise in the area, while sometimes such an expertise only adopts a theoretical perspective.

Most of the abovementioned start-up characteristics have been corroborated in the present analysis. To move beyond these acknowledged and well-established assumptions, we have utilised a methodology that, applied to the brain technology domain, allows the study of the profile and behaviour of European brain start-ups in detail. The methodology tried to find evidence that proves that the current activities of the start-ups are well aligned with the European ambition of putting in place cutting-edge tools that facilitate technology advances in the fields of neuroscience, computing, and brain disorders medicine.

In particular, the methodology used in this analysis is based on the *Discover*, *Design* and *Deliver* phases of Design Thinking, and have implied the interaction of the HBP Innovation team with stakeholders and start-up representatives. A scheme of this methodological sequence is described in figure 1.

Figure 1. Methodology



The *Discover* phase required a very intensive cognitive immersion in the problem addressed. After defining the objectives of the analysis, a 360º research process has been undertaken to guarantee an environmental scanning and in-depth searching of multiple data sources. A selection and mapping of the most active technology-based start-ups operating actively in Neuroscientific, Neurocomputing and Neuro-medical areas have been carried out by a team of seven analysts. Once the non-

European companies have been removed, all the information has been further cleaned and depurated.

The *Design* phase of the analysis demanded an exercise of evaluation and synthesis of the information collected. Only start-ups younger than 10 years old have been considered in the study, which have finally implied a systematic and detailed observation of 221 companies. The analysts have individually studied each company from the perspective of innovation and the alignment of its tools with the services offered by EBRAINS. More specifically, the following aspects have been gathered, recorded, and analysed in every company:

- Company name and contact data: email, website, contact person
- Country of origin
- Size of the company: staff and sales
- Age of the company
- Geographical scope
- Problem(s) that the firm tries to solve
- Number of patents and/or licenses owned
- Current customers
- Main projects where the company participates
- Industrial partners
- Academic collaborations
- Matching with EBRAINS services
- Perceived strengths and weaknesses
- Innovativeness, novelty of the solutions

The *Deliver* phase of the work implied the elaboration of the report and the justification of conclusions. The dynamics of the European start-ups landscape necessarily implied the presentation of our insights and advice with a very practical and policy-oriented perspective. In this sense, the HBP researchers and technology developers´ feedback and approval has been crucial for further refinement prior to dissemination.

1. BRAIN-TECHNOLOGY START-UPS: PROFILING

A structural problem that start-ups companies generally must face - not only within the brain technology sector but also in other domains - is a rather limited access to financing solutions and capital. The access to funds depends on a variety of factors and have important implications for the management of these companies. Such a common and critical problem explains why we have decided to include the funding discussion in the starting part of this profiling.

The great difficulties encountered by the start-ups to get external funding actually justifies the very frequent funders´ decision to compromise their personal financial resources. In this respect, they tend to use very intensively, and quite reasonably, any endorsements they receive from big players, recognitions, and awards as a practical and convincing way of communicating and capturing the attention of future investors. For further financial and strategic decisions, they are very frequently - and often informally - supported by business advisors or scientific boards.

Our analysis has revealed that a large part of the European start-ups (62%) is inclined towards a private type of financing, showing in general and a lower role of the public or mixed sector (see figure 2). The most frequent private funding option found in our start-up sample is venture capital. Apart from venture capital, other modalities like bank lending, crowdfunding, equity financing, and business angels are considered private funding in this report. Other informal funding options have been found in our analysis that basically rely on bootstrapping, family, and friends´ economic support.

As for the public funding offer, e.g., funding initiatives promoted by the European Commission and covered by the current Horizon Europe, we also noted that the fast-growing demand for funds from innovative projects has by far exceed the initial EC available capital volume.

As an example, the Commission’s budget for EIC Accelerator funding[11] -previously represented by the SME Instrument- approached about 1.1 billion in April, while the total number of applications was around 4.85 billion in June, from 2,000 start-ups[12].

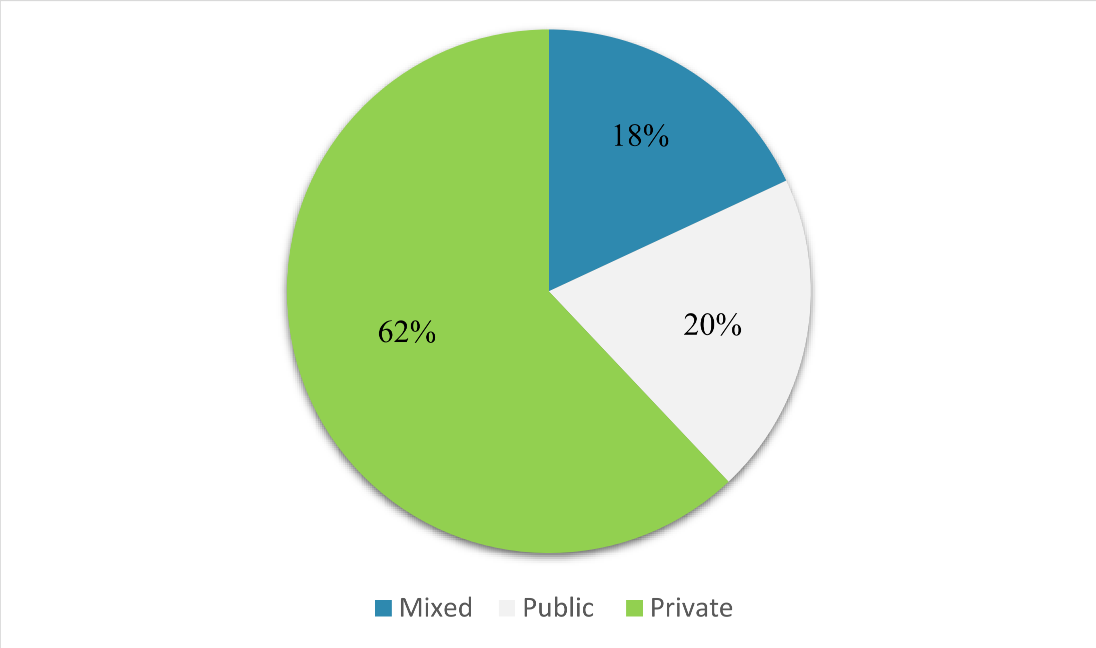
This is a problem that has been dragging on since previous funding periods and have undoubtedly affected the beginnings of the European start-ups. In this sense, efforts

11 https://eic.ec.europa.eu/eic-funding-opportunities/eic-accelerator

12 https://eic.ec.europa.eu/news/eic-accelerator-cut-statistics-2021-06-22_en

have been intensified on programs adapted to the dynamics of the start-up ecosystems (where project leaders, investors, SMEs, agencies, and small companies interact), trying also to diversify the public funding offer not only through priority themes (Strategic Digital and Health Technologies or Green Deal challenge[13]) but also with an entrepreneurial perspective that helps novel companies, for instance, in terms of planning, mentoring and award recognitions.

Figure 2. Funding modality chosen by the start-ups analyzed



From a global perspective, technology-based start-ups seem to be favored in highly competitive markets such as the United States or China. Evidence of this is the concentration of unicorns in these countries and their limited presence in Europe (Kaya et al, 2016). The difficulties found by technology creators to easily access to financing in early stages led the EC to launch new proposals through venture capital funds in cooperation with private funds[14]. In the brain technology domain, it is very likely that a boost of both public and mixed funding contributions for emerging projects will happen in the coming years.

The funding discussion may also lead us to analyze to what extent the European start-ups are able to finance their investments with their operational revenues and benefits. In this sense, we observed that start-ups most frequently do not offer public information about their sale volumes. From the brain start-ups that transparently project and publicly provide such information, we noted that most of them (see figure 3) are moving in the range of €1 MM to €10 MM sales per year (23%), being concentrated in countries such as France, Spain, Switzerland, UK, and

13 https://eic.ec.europa.eu/eic-funding-opportunities/eic-accelerator_en

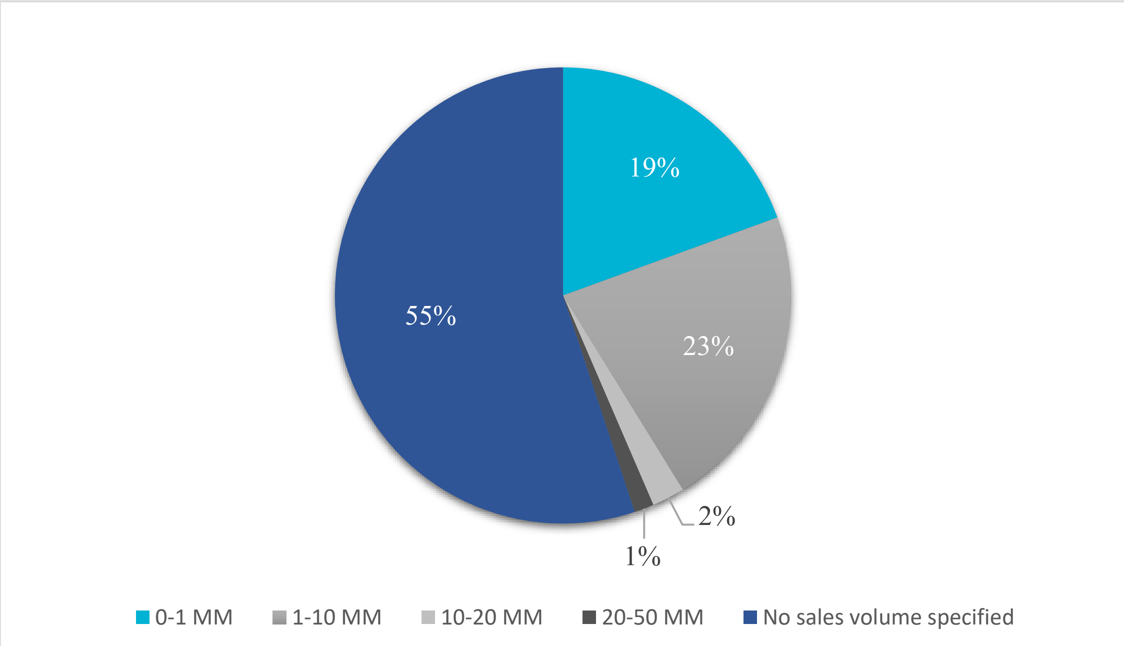
14 https://www.reuters.com/article/us-portugal-websummit-eu-idUSKBN1331HR

the Netherlands. Within this segment, we can mainly find technologies related to artificial intelligence for the diagnosis, prediction and treatment of brain and respiratory diseases, drug development and neuroimaging. Another factor we observed is the growth shown by entrepreneurial initiatives with less than five years of experience in the market, which are largely driven by mixed-type funding modalities (public and private capital) and less frequently supported uniquely by public funding programs. In addition, most of these companies are inclined to licensing, as a form of technology transfer and commercialisation, rather than patenting.

Another group of companies identified are those that have sales up to one million euros per year (19%), being basically concentrated in Spain, Germany, France, and Belgium. In this segment, multiple solutions could be highlighted from the neuromonitoring, pharma, neuroimaging, or neurosurgery technology areas.

Start-ups whose sales volume is above €10 MM represent a very small percentage (2%) and present a limited participation in countries like France, UK, Belgium, and Serbia, with a predominant focus on neuromonitoring solutions.

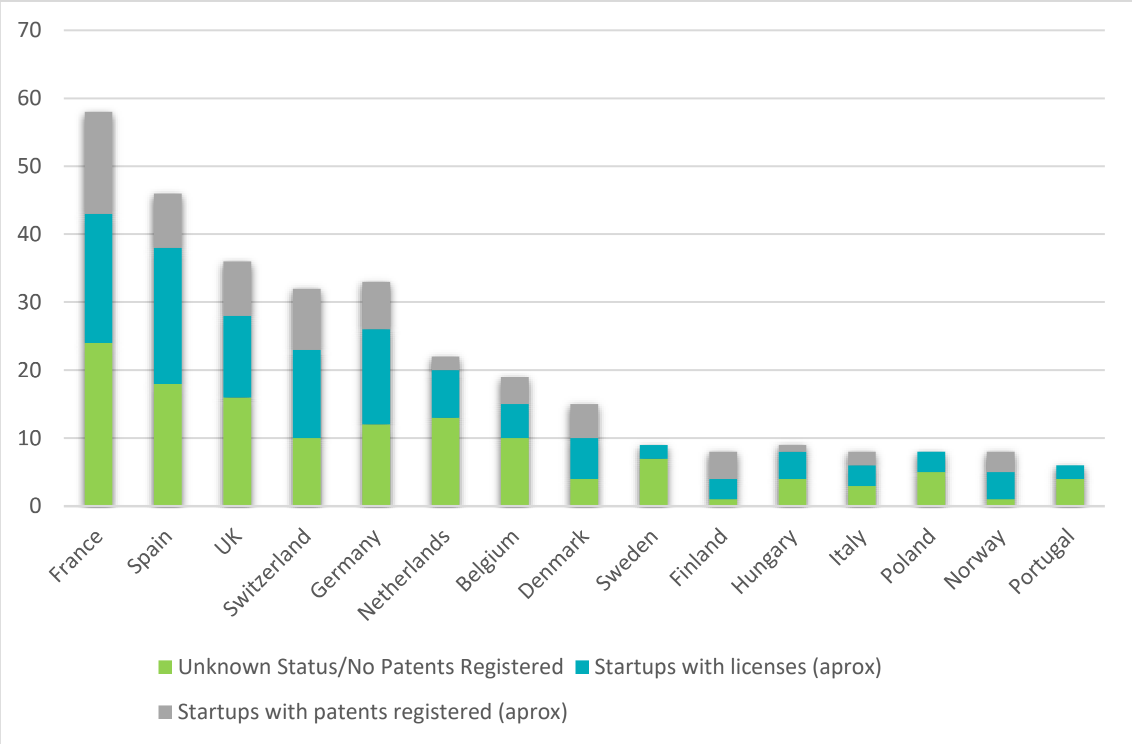
Figure 3. Start-ups annual sale volumes



Only a small percentage of companies (1%) has managed to become European references, with outstanding solutions in pharma, neuromonitoring and neuroimaging, and showing a relevant sales volume exceeding €20 MM per year. They are companies that successfully positioned themselves in the industry within a short period of around five years. They have international presence, as well as broad and multidisciplinary human resources. Another noteworthy aspect of this segment is its innovation performance compared to other firms resulting in attractive investments for venture capital and offering very practical and useful tools for specialists. Some of them have created instruments for helping surgeons worldwide to perform virtually target surgeries. Other ones already represent an interesting positioning in the drug industry by combining AI algorithms and computational development of drug components.

More than half (55%) of the European start-ups investigated do not specify sales volume. In many cases, these are projects that, due their early stage, are still involved in clinical trial phases, looking for venture capital options, or immersed in seed funding processes. This group is mainly located in France, Spain, UK or Switzerland. Selling licenses or patents is a funding option for these companies. Figure 4 shows that licensing is more broadly utilised protection and exploitation modality (principally software licenses) than technology patenting.

Figure 4. Start-ups' preferred protection options



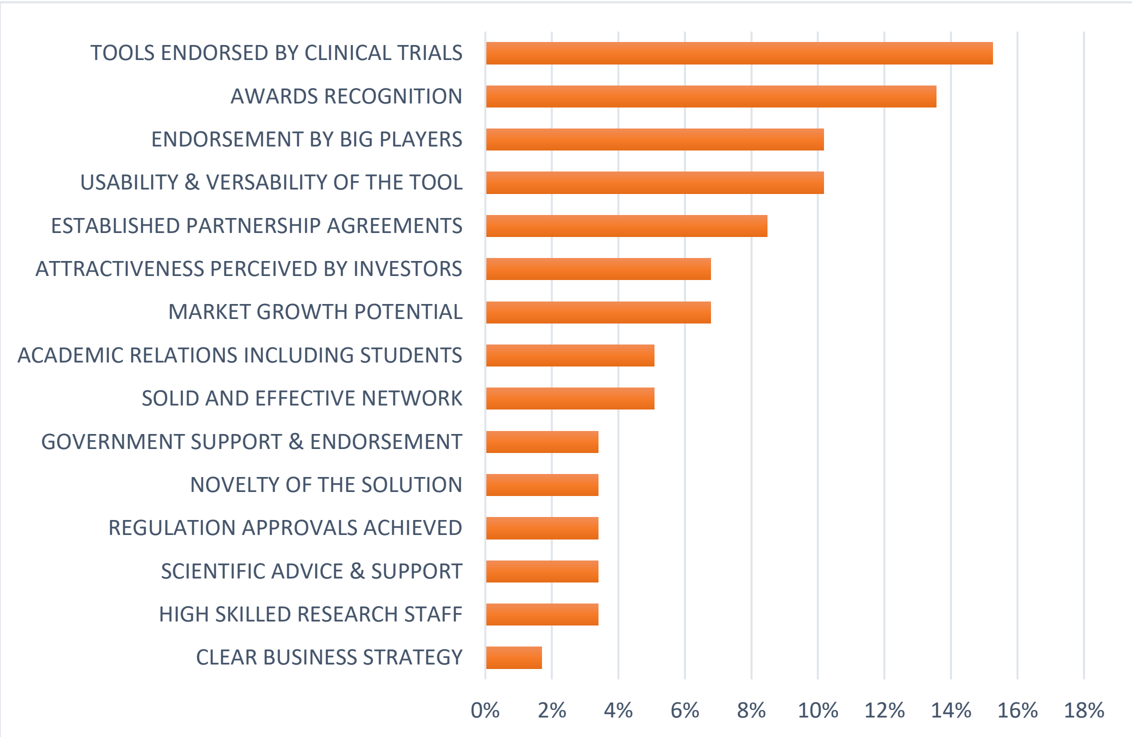
Multiple factors may explain this preference. Unlike other markets such USA, in Europe the processes for legal registration and grating of software patents are far from having unified criteria, with lengthy procedures that seems to be more common and favourably assumed by the telecommunications industry (Thumm, 2017). Long time is needed to harmonize these protection systems, and to update them to continuous digital changes. In this regard, the European Commission is accelerating efforts to protect not only software patents, but also other types of intellectual property that are becoming increasingly relevant such as GUIs, icons, industrial designs, 3D printing, etc., already considered as "strategic assets for firms"

(EC, 2020). Such protection services at the European level will benefit the adaptation and competitiveness of the start-ups within the international markets.

Funding decisions, from the start-up perspective, depend in sum on multiple factors. To complement the discussion on the funding problem, we have used our sample of 221 start-ups to identify their most evident strengths and weaknesses, many of which have direct influence on their capability to getting such a funding. They are strategic drivers that explain to a large extent why some successful histories within our sample have happened.

15% of the identified companies, for example, are taking good advantage and use of their successfully completed clinical trials processes of their tools (see fig. 5). Gathering evidence that their developed products and/or services effectively work in real environments, like hospitals, can be used to give credibility to the projects and improves the capital investors´ confidence. On some occasions such a confidence takes the form of recognitions (14%) and public endorsements (10%) and gives rise to contract agreements and joint-exploitation partnerships.

Fig. 5. Main strengths identified in (<10 years) European brain start-ups

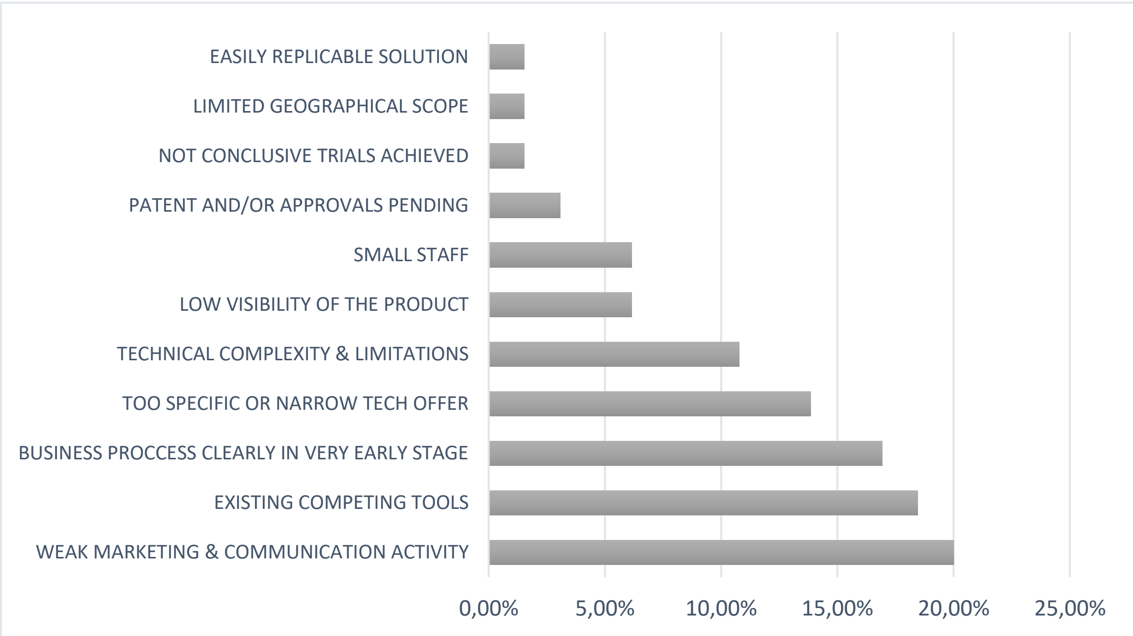


Other strength is related to the opportunities that young markets usually bring to companies, since incipient new markets are most frequently associated to highly relevant prospects for growth. Funding reticence may certainly disappear when there are clear and promising market expectations.

Established networks, including scientific contacts that usually gives altruistic advice and support, are also factors that make strategic management of start-ups more professional and increase the possibilities of obtaining financial support. Our analysis proves the importance of getting such an advice and support, as less than 2% of the analysed start-ups show a defined business strategy.

A quick analysis on weaknesses (fig. 6) reveals that around 20% of the start-up companies identified have not very effective marketing and communication plans. Wrong or weak communication actions make the start-up operations - and their products or services - invisible for users and may transmit an unattractive corporative vision of the company to venture capital firms and potential investors.

Fig. 6. Main weaknesses identified in (<10 years) European brain start-ups



A threat also detected in the 18% of the analysed cases, and with potential to alter many funding decisions, is the existence of alternative and competing tools in the market. Since investors always look for profitability and novelty of the offered solutions, the start-ups must work with a clear and determined direction towards product differentiation. Finally, other aspects, like technical limitations, excessive complexity of the product, or companies owning a very specific or narrow offer – all these aspects are present in more than 20% of the studied initiatives - reduce the market niches and may definitely dissuade future investors.

2. WHERE IS BRAIN INNOVATION HAPPENING?

The results disclosed in this section respond to an exhaustive mapping work and give answer to the question "Where?" from two different perspectives: firstly, we will recognise where European start-ups are innovating more intensively (technology areas); then we will try to understand where European start-ups are innovating more intensively, in geographical terms.

As for the first perspective, our analysis has proved useful to identify 12 different areas of work where the analysed European start-ups are working more intensively (see figure 7). Importantly, these categories have been inductively revealed (bottom-up) from the observation of the empirical data and only defined after a clustering analysis. The 12 categories have been then classified according to other 62 identified sub-categories as described in table 1 and 2. When a company showed operations in different categories, the category used to label that company in our analysis corresponds to its principal area of work.

We can observe in table 1 and figure 7 that more than 50% of the analyzed European start-ups are focused in Neuropharma development, Artificial intelligence solutions for Neuromedicine, and Neuromonitoring tools for brain health. Neuroimaging and Neurostimulation (both invasive and non-invasive) are areas that together capture the attention of around 20% of the start-ups operating in the area. Finally, there is a variety of developments – new diagnosis methods, Biomarkers, Virtual reality, Neurorobotics, Data analysis, Surgery, and Genetics – that represents the 30% of the ongoing technologic advances in the start-up landscape.

Figure 7. Brain technology categories

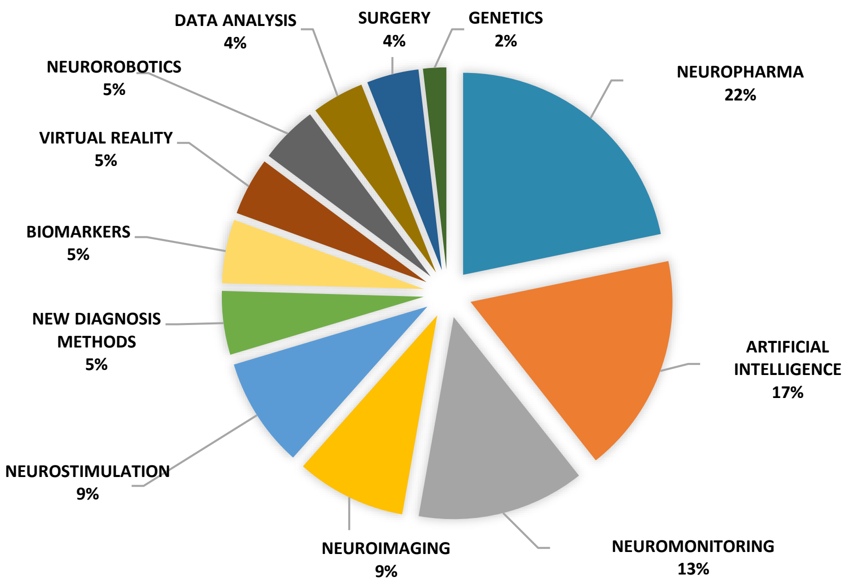


Table 1. Brain technology categories and sub-categories identified in the analysis

TECHNOLOGY CATEGORY	TECHNOLOGY SUB-CATEGORY	
NEUROPHARMA	• COMPUTATIONAL APPROACH TO DRUG DISCOVERY • DELIVERY OF DRUGS • MOLECULES DEVELOPMENT • NEUROPHARMA GENERAL SOLUTIONS • SUPPORTING & AUXILIARY METHODS FOR NEUROPHARMA	**22%**
ARTIFICIAL INTELLIGENCE	• AI GENERAL SOLUTIONS • AI SEMANTIC DATA • AI SPECIFIC TOOLS FOR ALZHEIMER DIAGNOSIS • AI-BASED DIAGNOSIS • AI-BASED TELERADIOLOGY • AI-BASED TOOLS FOR INTENSIVE CARE UNITS • ALGORITHMS FOR DIAGNOSIS • GRAPH AI • MACHINE LEARNING INFRASTRUCTURES • MACHINE LEARNING SOLUTIONS	**17%**
NEUROMONITORING	• BIOSENSORS & INTERNET OF HUMANS • BRAIN MONITORING • DIGITAL MEDICINE • DISEASE MANAGEMENT • DRUG PRESCRIPTION TOOLS • EEG ANALYSIS • EPILEPSY MONITORING TOOLS • ASSESSMENT OF EPILEPTIC PATIENTS´ DATA • BRAIN HEALTH GENERAL MONITORING • PARKINSON MONITORING TOOLS	**13%**
NEUROIMAGING	• BRAIN PET • DATASETS - IMAGES • MICROSCOPY • NEUROIMAGING	**9%**
NEUROSTIMULATION	• BIOELECTRONIC MEDICINE • DEEP BRAIN STIMULATION • ELECTRICAL STIMULATION • IMPLANTS & NEUROMODULATION • NEURAL INTERFACES • NEUROPROSTHESIS • NEUROSTIMULATION	**9%**
NEW DIAGNOSIS METHODS	• ACOUSTIC TECHNIQUES • BRAIN PRESSURE DIAGNOSIS • OCULAR DIAGNOSIS • TISSUE ANALYTICS	**5%**
BIOMARKERS	• BLOOD ANALYSIS DIAGNOSIS • EPILEPSY DIAGNOSIS • GENERAL BIOMARKERS • SAMPLE PREPARATION	**5%**
VIRTUAL REALITY	• E-LEARNING • GAMING AND VIRTUAL REALITY FOR BRAIN HEALTH • NEUROGAMES • VIRTUAL REALITY FOR PRE-INTERVENTION • VIRTUAL REALITY FOR REHABILITATION	**5%**
NEUROROBOTICS	• BRAIN COMPUTER INTERFACES • MACHINE VISION • NEUROREHABILITATION HARDWARE • NEUROROBOTICS	**5%**
DATA ANALYSIS	• DATA ANALYSIS • DATA CURATION	**4%**
SURGERY	• BRAIN CANCER SURGERY • EPILEPSY SURGERY • SURGERY AND CLINICAL TRIALS AI TOOLS • SURGICAL MICROROBOTS • VIRTUAL REALITY FOR SURGERY	**4%**
GENETICS	• GENE THERAPY • GENETIC DATA ANALYSIS	**2%**

Table 2. Brain technology categories definitions

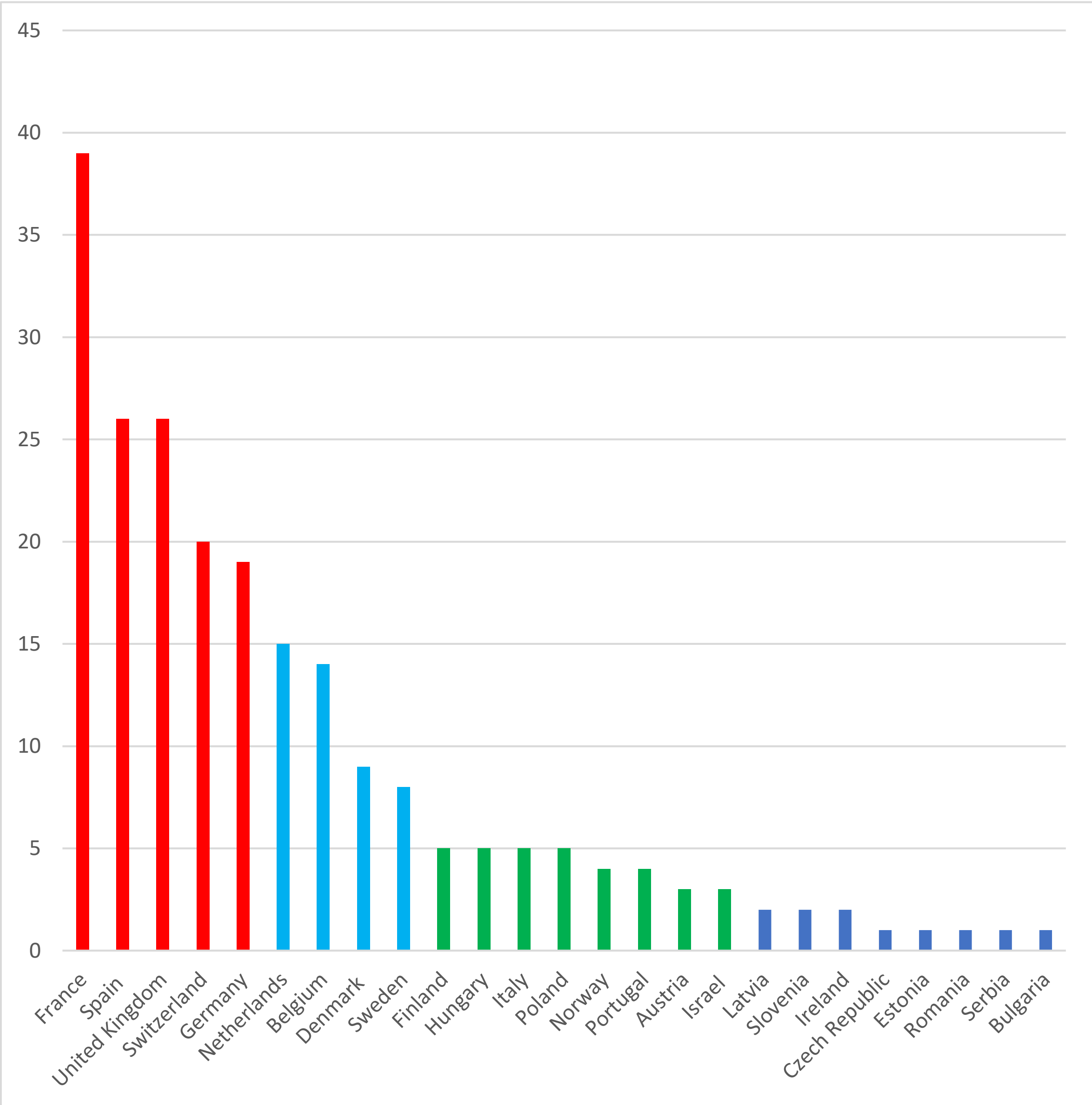
NEUROPHARMACOLOGY	Neuropharmacology can be defined as the study of psychotropic drugs that affect nervous tissue. As such, the domain of neuropharmacology includes psychotropic drugs that affect mood and behaviour, anaesthetics, sedatives, narcotics, anticonvulsant, analgesics, and a variety of drugs that affects the autonomic nervous system (Polich & Criado, 2006)
ARTIFICIAL INTELLIGENCE	Artificial Intelligence (AI) is a general term that entails the use of a computer to model intelligent behaviour with minimal human intervention. As such, Artificial intelligence (AI) is defined as "a field of science and engineering concerned with the computational understanding of what is commonly called intelligent behaviour and the exploitation of such understanding" (Shapiro SC. (ed) Encyclopedia of Artificial Intelligence, vol. 1, 2nd ed. New York: Wiley, 1992). With respect to the medical field, AI can be exploited through a wide scope of possibilities such as Robotics, medical diagnosis, medical statistics, and human biology. These technologies aim to support healthcare workers and physicians in their medical duties, assisting with tasks that rely on the manipulation of data. Such systems include Artificial neural networks (ANNs), fuzzy expert systems, evolutionary computation and hybrid intelligent systems.
NEUROMONITORING	Neuromonitoring can be defined as a subcategory of medical field to make individualized management decisions in order to prevent secondary brain injuries and avoid surrounding complications. Traditionally, neuromonitoring has consisted of a combination of clinical examination, neuroimaging and intracranial pressure monitoring (Makarenko et al, 2016). However, nowadays neuromonitoring applications range from being able to not only identifying second insults or intracranial complications -such as haemorrhages, increase in ICP, etc. - but also to guide the clinicians along medical management. Recent advances in multimodal neuromonitoring have allowed the evaluation of changes in markers of brain metabolism -such as glucose, lactate, pyruvate, and glycerol- and other physiological parameters such as intracranial pressure, cerebral perfusion pressure, cerebral blood flow, partial pressure of oxygen in brain tissue, blood pressure, and brain temperature (Feyen et al, 2012)
NEUROIMAGING	Brain imaging has become a core technical element of the clinical patients with neurological and psychiatric diseases. Neuroimaging helps to understand how the brain and the other parts of the nervous system are working and what structural or functional alterations may be associated with a specific clinical medical condition. To reach this goal, the approach needs to be addressed both from a clinical and in a neuroscientific approach. These technical tools and applications represent new approaches to the nervous system's organization (Filippi et al, 2012), its pathology in disease and its biological markers.

NEUROSTIMULATION	Current advances in neurostimulation technologies are changing neurologic and psychiatric medical fields. Neurostimulation therapies include invasive and non-invasive approaches that involve the application of electrical stimulation to drive neural function within a circuit. These implantable neurostimulation systems target specific deep subcortical, cortical, spinal, cranial, and peripheral nerve structures to modulate neuronal activity. In this sense, recent research demonstrated that patients with failed back surgery syndrome and complex regional pain syndromes benefit significantly from neurostimulation in pain reduction, functional capacity, and quality of life (Graham et al, 2021). Increasing clinical evidence indicates that neurostimulation offers less invasive and more effective therapies for many patients with ischemic pain caused by cardiovascular and peripheral vascular diseases (Rosellini et al, 2011)
NEW DIAGNOSIS METHODS	Early diagnosis is crucial for understanding the evolution of diseases. The latest advances in medical technology aim to provide physicians and supply health - infrastructures with the latest tools in clinical diagnosis. New diagnosis methods strive for both an earlier and more accurate diagnosis and result on a remarkable better prognostic, more efficient and accurate. Applications of new diagnosis methods range from clinical settings to the daily responsibilities of health workforce, medical labour and physicians.
BIOMARKERS	The term "biomarker" can be defined as a vast subcategory of medical objective indications and signs that can be measured accurately and used by physicians on clinical field (Working Group Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Therapeutics. 2001;69:89–95) In a recent report regarding the validity of biomarkers in environment risk assessment, the WHO (2001) has stated that a true definition of biomarkers includes "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological". As such, biomarkers are objective medical signs (as opposed to symptoms reported by the patient) used to measure the presence or progress of disease, or the effects of treatment. Biomarkers can have molecular, histologic, radiographic, or physiological characteristics. Examples of biomarkers range from basic pulse and blood pressure to more complex laboratory tests of different tissues. In this sense, biomarkers can provide information not otherwise accessible by a more conventional source of information, such as medical records, surveys, or vital statistics.

VIRTUAL REALITY	Virtual reality (VR) can be described as the technology that allows physicians to simulate a situation or experience of interest, within an interactive but computer-generated environment. The simulation is immersive and may require the use of special devices in order to help the user learn from experience in this virtual world. Virtual reality medical simulations can be of use in a wide scope of possibilities, ranging from self-directed learning - allowing trainees to develop skills at their own pace and allow unlimited repetition of specific scenarios that enable them to remedy skills deficiencies in a safe environment - to fields relating to computer vision (Rosen, 1992), graphics and Robotics (Altobelli et al, 1993).
NEUROROBOTICS	The interdisciplinary field of neurorobotics looks to lead and build artificial intelligence and cognitive systems allowing physicians to revolutionize medical care. Neurorobotics is a relatively recent innovation in the field of medicine and is of particular interest for surgeries and interventions requiring minimally invasive procedures (Najarian et al, 2011). Neurorobotics has done considerable advancement in such surgeries, due to its refined precision, stability and dexterity.
DATA ANALYSIS	The term "Data analytics" relates to the accumulation and consequent analysis of vast quantities of data, which after being analysed, its essential insights are drawn from the information contained and used. Hospitals increasingly use data analysis to keep an eye on overall hospital performance and track aspects like patient progress and outcomes, track bed occupancy, improve bedside and ICU care, and offer the opportunity to improve general inefficiencies. Biomedical research also generates a significant portion of big data relevant to public healthcare. The aim is to create a strong integration of biomedical and healthcare data, so that modern healthcare organizations can revolutionize the medical therapies and personalized medicine.
NEURO SURGERY	The latest technological developments in imaging guidance, neuro, and micro robotics and microscopy have led neurosurgeons in particular and physicians in general to push the limits of what was once achievable. This multidisciplinary medical subcategory benefits from a range of medical specialties, such as AI and Neurorobotics. The introduction of robotically assisted surgery has provided surgeons with improved ergonomics and enhanced visualization and dexterity, allowing them to perform the most arduous procedures with state-of-the-art technologies.
GENETICS	Human gene therapy is a medical specialty focusing on the modification or manipulation of the expression of a gene or the alterations of the biological properties of living cells for therapeutic use. Human and molecular genetics have made remarkable advances recently in developing an understanding of human biology in health and in disease. The rapidly developing tools of gene therapy and genome editing are quickly opening up new possibilities in the medical field.

The second perspective is related to the main geographical location (headquarters) of the (<10 years) European start-ups. Our sample indicates that a very significative proportion (close to 60%) of these brain-technology companies are based in France, Spain, United Kingdom, Switzerland, and Germany (see figure 8). Other very active countries in brain technology are the Netherlands, Belgium, Sweden, and Denmark, which jointly represent around 20% of the brain-start-up activity. The group formed by Hungary, Italy, Poland, Norway, Portugal, Austria, and Israel are developing very interesting advances while still represent together around 15% of the European start-ups´ activity. The remaining 5% of companies identified are originally set up in Latvia, Slovenia, Ireland, Czech Republic, Estonia, Romania, Serbia, and Bulgaria, and show still a low number of initiatives in the area.

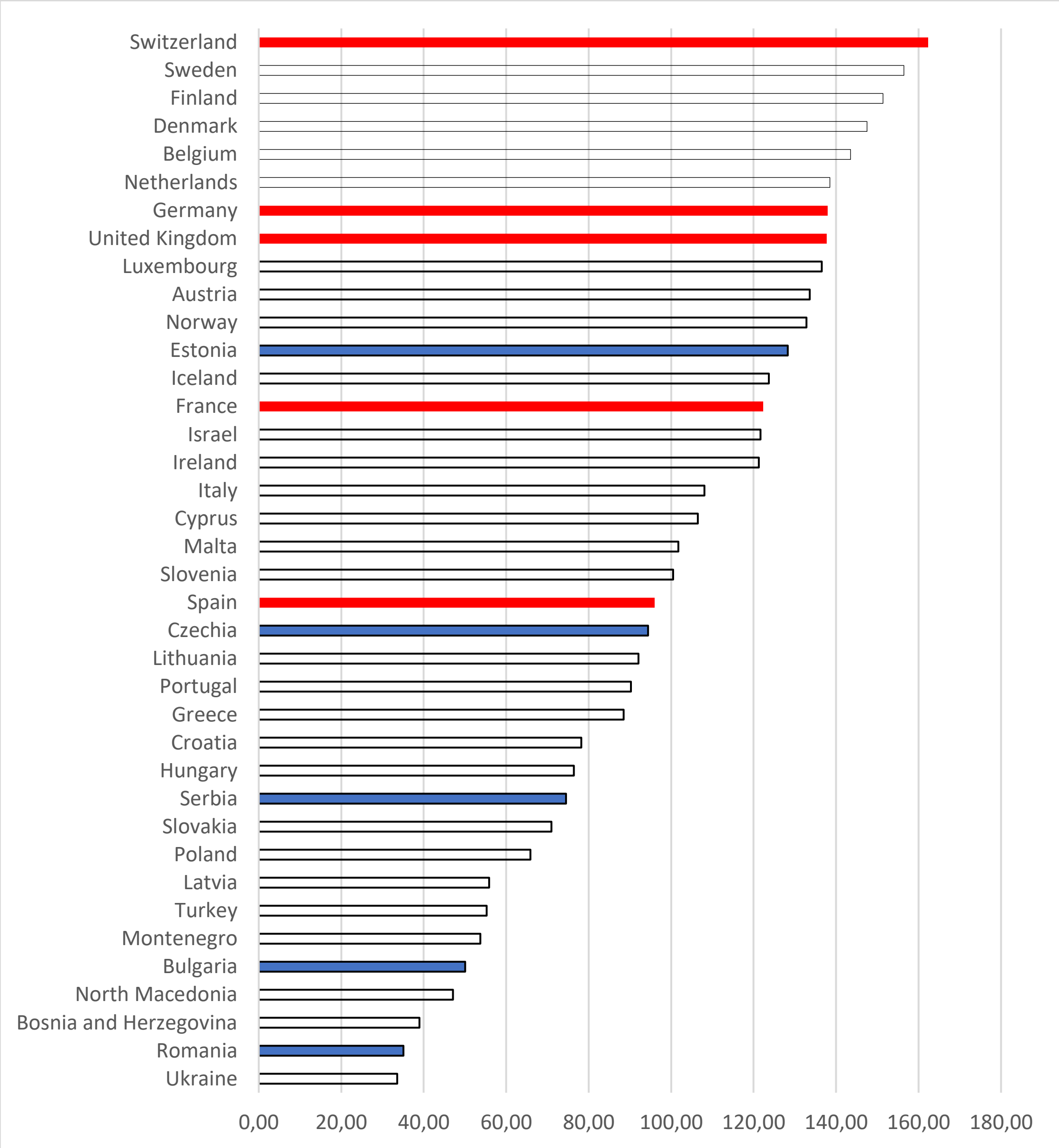
Figure 8. Number of start-ups identified by country of origin



There is a correlation between the number of active start-ups in each country and the overall innovation performance, which is given by the Summary Innovation

Index (figure 9) of the European Innovation Scoreboard (EIS). The index is based, among other variables, on the European countries´ framework conditions for entrepreneurship and innovation activities and the adequate context for firm investments.

Figure 9. Summary Innovation Index (European Innovation Scoreboard 2021)

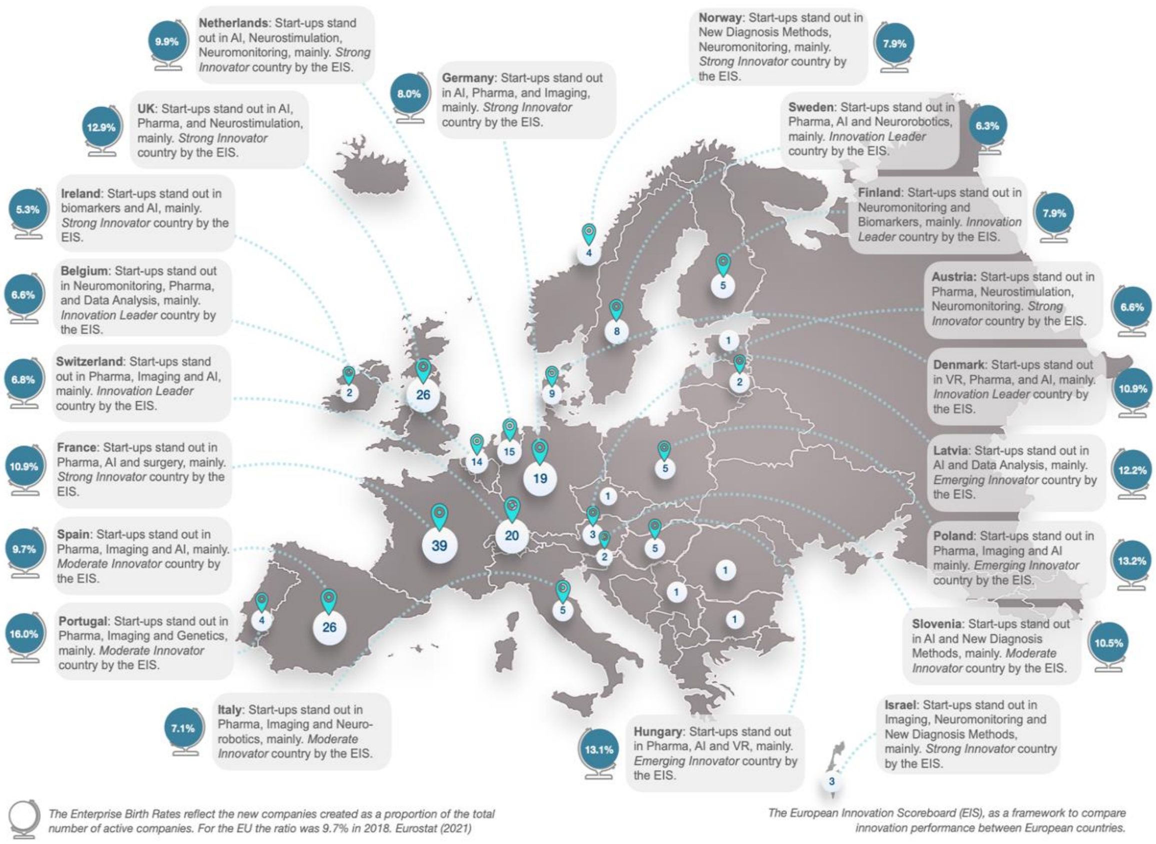


Source: European Innovation Scoreboard 2021

In fact, European countries with emerging start-ups and dynamic entrepreneurial projects in the brain technologies domain, like France (*strong innovator* according to the EIS), Spain (*moderate innovator*), UK (*strong innovator)*, Switzerland (*innovator leader*), and Germany *(strong innovator)*, present in parallel the highest innovation indexes. On the other side, lagging-behind countries – in terms of start-up activity - show the lowest scores in the scale.

A crosscutting analysis of the geographical locations and the technology areas on which the start-ups more intensively operate has been also elaborated by the HBP Innovation team to have a big picture on the brain-innovation potential and fields of specialization of each country. The figure 10 illustrates the result of this study and visually describes how countries are technologically positioned in the European landscape.

Figure 10. Number of brain start-ups identified and their main areas of specialization



Next section of this report will present an in-detail mapping of the technology categories and subcategories identified. Each technology field is described, and practical examples are included to understand the innovation performance of the start-ups in the area, market objectives and motivations.

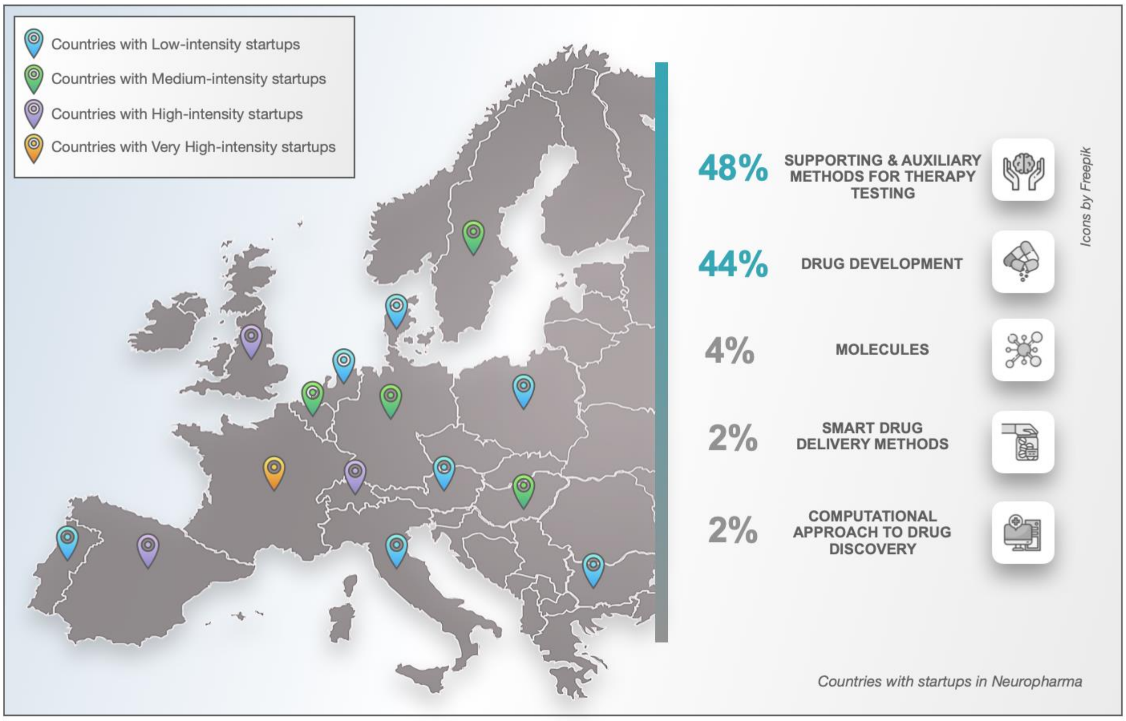
As many analyzed start-ups will surely become relevant actors of the future European research and innovation ecosystem, the descriptions and reflections included in the following section may also serve to predict what may be the evolution and dynamics of each brain-technology category across the European regions in the middle and long term.

3. START-UPS PERFORMANCE IN BRAIN-TECHNOLOGY KEY AREAS

3.1. NEUROPHARMA

From drug discovery to the delivery of drugs, companies in this sector make use of both biotechnology tools and chemical sources to develop their medical research and technology development. The integrated set of technologies mentioned in this section could be somehow regarded as the foundational structure of the European neurotechnology, the pharma market. Countries with higher activity[15] in this area are described in fig. 11.

Figure 11. Start-ups intensity in the Neopharma area



Advances in the area should serve to improve therapeutic effectiveness in clinical fields, notably in terms of establishing their combined potential for creating novel therapeutic remedies, e.g., by utilising computational approaches to drug discovery or by the generation of new molecules, among other applications.

15 As a reference for the Start-ups intensity (figure 11), note that in our analysis a “Very High-intensity” activity corresponds to more than eight specialised start-ups working in the area in that country.

Technological progress in hardware and software performance, algorithms design, and new biological advances for identifying new drug targets make computer-assisted tools highly useful in pre-clinical research. Computer-aided drug design contributes to reduce the experimental use of animals in vivo testing, help the design of safer drugs and repositioning of known drugs, and assist medicinal chemists in each step (design, discovery, development, and hit-optimization) of the drug discovery process.

In this context, **GAIN THERAPEUTICS SA**[16], a company created in the United States in 2017 and based in Switzerland, is redefining drug discovery through their novel technologies. Their goal is to unlock new treatment options for difficult-to-treat disorders characterized by protein misfolding. Protein misfolding is an underlying biological issue of many diseases, including lysosomal storage disorders and some neurodegenerative diseases such as Parkinson's disease. The company believes that if the misfolded enzymes (mutant or wildtype) are guided back into their functional 3D shape, the catalytic reactions can be reignited and the toxic substrate buildup that causes many diseases can be therefore eliminated. For this purpose, they have created *"See-Tx™"*, a Site-Directed Enzyme Enhancement Therapy computational platform that uses the published 3D structure of enzymes and a proprietary computational technology to discover new allosteric binding sites and predict their draggability.

The output from the See-Tx™ platform are newly discovered binding sites that for the first time, can be targeted for therapeutic benefit to correct enzyme misfolding, thus restoring function and eliminating the subsequent toxic substrate buildup that causes disease. Following site identification through the *See-Tx™* platform, the company uses proprietary structure-based computational methods to scan a library of small molecule compounds to fit the target site.

This method results in efficient and inexpensive candidate compound identification, after which the company conducts medium-throughput assays to identify novel, final lead program candidates. Because these compounds are denominated Structurally Targeted Allosteric Regulators (STARs), they do not interact with the enzymes 'active sites, enhancing both safety and efficacy. Because STARs are small molecule therapies, they have several significant advantages over the current standard of care for disorders associated with protein misfolding, including enzyme replacement therapy and gene therapy. They can be administered as a simple oral pill, can reach organs and tissues that are not accessible through current therapeutic

16 This section includes numerous references to specific companies (firm name and country of origin) working in the brain technology domain or, in some cases, providing broader health solutions with eventual application to brain disease. The selection of examples throughout the report is based on the relevance of the companies operation for the topic addressed.

options (including the brain, bone, and cartilage), and are easy and cost-effective to manufacture.

The revolution of organic synthesis has transformed the pharmaceutical industry, as it has allowed companies to produce any targeted molecule in nearly all therapeutic areas. In recent years, Biologics research has been at the forefront of drug development, offering treatment for many medical conditions that have not found yet other therapy alternatives. **FREEOX BIOTECH** is a Spanish company founded in 2017 with the objective of discovering and developing medicines to reduce the effects of the oxidative stress in the organism, and especially those related to the neurological and cardiovascular system. Focusing mainly on strokes, their approach draws on the knowledge of oxidative stress and uric acid, and they are developing neuroprotective therapies to reduce the damage resulting from ischemia. Mainly focusing on strokes, they have created and developed two leading products. The first. one, called *Ox-01* is Uric Acid used as a medicinal product. *Ox-01* has a proven effect in preventing the damage caused by reperfusion after stroke. The company has completed clinical trials with *Ox-01* until phase IIb (with 421 patients) demonstrating good safety and tolerance profile, and statistically significant efficacy as a neuroprotectant in stroke. Ox-02 is a molecule resulting from the association of Ox-01 and Citicoline, being currently under preclinical stages.

Another interesting approach can be found in **SYNDESI THERAPEUTICS**, a Belgian company founded in 2018 that develops molecules which act through a novel mechanism to modulate synaptic transmission. When synaptic dysfunction occurs, the consequent disruption of connectivity between brain regions underlies the cognitive and psychiatric symptoms of Alzheimer’s and other disorders with cognitive impairment. Their molecules act in a unique way on the synaptic vesicle protein SV2A. SYNDESI has an exclusive license for its molecules and technology from UCB, the leading company in SV2A research. UCB developed two major marketed products that modulate SV2A, the anti-epileptic drugs levetiracetam (*Keppra*®) and brivaracetam (*Briviact*®). SYNDESI’S pro-cognitive SV2A modulators regulate the function of SV2A in a distinct manner, showing pro-cognitive but not anti-epileptic properties in preclinical models.

Companies such as **PERHA PHARMACEUTICALS** are specialized in developing protein-based drugs that affect cognitive disorders related to Down syndrome and Alzherimer’s disease, in addition to other conditions such as hearing loss, polycystic kidney disease and ischemic strokes. The group explains that Down syndrome is the most frequent genetic cause in cognitive diseases, focusing their studies on kinases or regulatory enzymes of protein cells involved in these conditions, such as DYRK1A which acts as an inhibitor, and which also has efficacy on AD. A differentiating aspect with respect to start-ups in this area is that they use marine resources for the development of drugs in the initial phases such as the marine sponge or leucettamine B. In addition, after conducting mouse trials for both AD and Down syndrome conditions, they were able to identify the inhibitor leucettine 21 (Lan Nguyen, 2018) among hundreds of them. Their next preclinical trials will begin between 2021 and 2022.

From a broad perspective, we can see that brain pharma start-ups are obviously engaged to the creation of first in class formulas addressing important medical needs in the field of neurodegenerative diseases. The objective is curing neurological disorders by developing innovative treatment strategies based on a new class of orally available compounds. Several technologies have been successfully developed and most of them are already accessing the market and available for clinical use. We will now showcase latest technologies created to give solutions to three very relevant brain problems: brain cancer, neurological and neurodegenerative disorders, and mitochondrial disease.

On the one hand, resistance against cancer drugs is recognized as the major limiting factor to the long-term survival of cancer patients. **TOLREMO** is a Swiss company that brings a new wave of resistance-preventing precision therapies to patients with cancer. Their therapies aim to work in parallel to standard cancer therapies to offer better response rates, longer survival and an improved quality of life. In addition to combination therapies, they investigate their drug candidates for having efficacy as stand-alone agents in cancer indications of defined transcriptomes. On the other hand, most anticancer drugs used clinically (standard chemotherapy) lack any intrinsic selectivity, causing severe side effects as the result of their toxicity toward healthy tissues. **SEEKYO** is a biotech company developing a Smart Chemotherapy, selective to tumours and safer for patients. They are designing smart drugs that selectively target the microenvironment of solid tumours while sparing healthy tissues. The company´s unique technology comprises a molecular platform enabling the custom design of almost any type of therapeutic vector. This versatile linker technology offers the possibility to design "on demand" the most appropriate targeting assembly to treat a given malignancy, based on its unique tumour-associated specificities.

Neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS), etc. represent a major challenge for our society. Neurodegenerative diseases (NDDs) are currently incurable and bring severely impactful conditions due to progressive degeneration and death of nerve cells, resulting in devastating and often fatal problems of mental function and movement. Moreover, due to the Western population age, NDDs are becoming one of the most important epidemics of the 21st century and are supposed to double over the next 10-20 years (Gauthier et al, 2021).

There is therefore an urgent need for the development of non-toxic molecules with neuroprotective disease-modifying action, capable to treat and prevent a combination of these underlying mechanisms simultaneously. As NDDs are chronic diseases, the developed molecules need to demonstrate an exceptional safety profile allowing long-term treatments. The technologies developed by the start-ups analysed are trying to a large extent to address and overcome these troubling diseases. **CYPRALIS**, a British company founded in 2012 is developing a novel category of small molecule drugs that inhibit cyclophilins, a large family of proteins involved in many diseases. The company has IP rights on three distinct classes of small molecules that share potent inhibition of cyclophilins span a wide range of molecular weights, solubility, isoenzyme specificity and PK properties (including crossing the blood-brain barrier). These compounds are used as tools to validate inhibition of cyclophilins as novel therapeutic approach to treat diseases and as starting points for specific medicinal chemistry programmes.

The company **PRIAVOID** uses mirror-image-phage-display-selection and various optimization technologies to develop compounds composed exclusively of D-enantiomeric (mirror image) amino acids. Their all-D-peptide development platform enables the generation of lead compounds for any given target, especially for CNS disorders. In contrast to natural peptides consisting of L-amino acids, this new class of drug substances is resistant to proteases, permeate the blood-brain-barrier effectively, display very low immunogenicity and degradation profiles in vivo and are therefore suitable for oral drug administration. Many other companies are developing molecules that promise to simultaneously target the main underlying mechanisms of NDDs and demonstrate significant efficacy in the treatment & the prevention of NDDs.

Mitochondrial diseases, which occur when mitochondria (found within all cells of the human body and responsible for producing the energy necessary for life) is defective, result in a wide range of serious and debilitating illnesses. In this context, **KHONDRION**´s in-house discovery engine is using unique live-cell imaging technologies, patient-derived cell lines and predictive cell-based disease models to build a portfolio of promising compounds. Active discovery programs are underway developing new therapies, biomarkers, and new read-out technologies in the field of mitochondrial diseases.

As exposed above, molecular targets of neurodegenerative diseases are well identified, and drugs able to clear those targets developed in vitro. However, in vivo, drugs do not always pass through the Blood-Brain Barrier to get to the Central Nervous System. **NEUROSCIENCE INNOVATIVE TECHNOLOGIES**, a Spanish start-up, claims that the best approach to solve this problem is to rely on proprietary drug delivery systems based on implantable devices able to deliver drugs to the CNS. After minimally invasive surgery to get the device implanted, percutaneous access allows easy dosing for long term delivery of drugs with superior effectiveness and safety to conventional routes of administration.

Computerised simulation is also playing an increasingly important role in pharma processes and product development. Simulation processes however need to fully rely on the accuracy of physical property data. Given that experimental data are often unavailable or unreliable, accurately prediction of physical properties of molecules and mixtures is typically the most critical part of efficient simulation processes. That is why some start-ups are focused on developing proprietary biomedical data platforms and suite of tools (together with algorithms) for clinical analysis, drug combination, and analysis of indicators expansion. Automated phenotypic screening and sequencing are also being used to identify and validate pathogenic proteins.

Quantum physics are also useful when it comes to halve cost and length of preclinical drug development. These companies work alongside Bio-pharma firms to transform the way drugs are developed and by moving from approximation to prediction. This sort of platforms allows the calculation of absolute free binding energy of molecules with the highest accuracy. Thanks to high performance computing resources and cloud accelerations, we can nowadays perform calculations up to a million times faster than in the past, thus allowing to find highly valuable compounds in large libraries with better chances of success than previous methods.

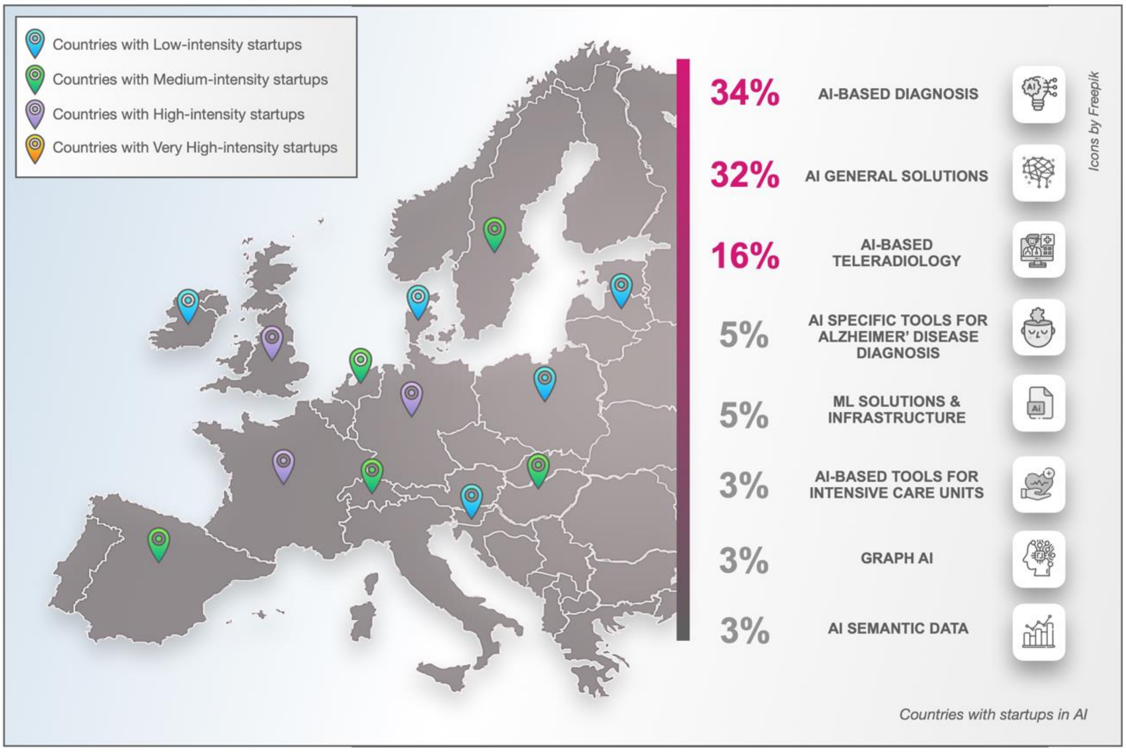
3.2. ARTIFICIAL INTELLIGENCE

Advances in computational power together with the massive amount of data generated in healthcare systems make many clinical problems ripe for AI applications. Some start-ups in the area, for example, produce, document, and deploy regulatory approved AI and machine learning solutions, with accompanying hardware. Services include image-related solutions for clinics, pharmaceutical, med-tech companies, and the research industry.

This sort of technologies varies from artificial intelligence platforms containing more than 30 million biomedical publications, clinical trials, side effect databases, to other solutions that enable the uploading, tagging, filtering and synchronization of datasets using secure files servers. As a result, physicians and clinical doctors can share data, AI models, and annotations with other members of their organization and promote a better collaboration in research and medical production. Countries with higher activity in this area are described in fig. 12.

The increasing application of AI to semantic data, in the same vein, is also explained by the cohabitation of more than 100 million patents, 70 million journal articles, and 4 billion web pages published, which create a vast corpus of information that potentially needs to be searched to establish, for example, the novelty of a product (essential requirement for patent filing), the state of the art in the field of interest, or the variety of components with-in complex compositions.

Figure 12. Start-ups intensity in the AI area



As an example, **SEMANTIC INTELLIGENCE**, a company founded in 2017, has developed an AI-driven IP Intelligence engine that enables scientists & IP experts to search, analyse, and extract complex knowledge on chemical-biological interactions, thus allowing them to spot the information they are looking for within more than 83% of the time required with current technologies. Their engine is built on a state-of-the-art AI technology set that combines Natural Language Processing. Machine Learning, Full linguistic data analysis, Chemical structure processing, and Image Recognition. Their technology represents first industry-level solution for automatic information extraction and data curation in pharmacology and biochemistry.

With a vision oriented to machine learning tools, **BIAS VARIANCE LAB** is a Slovakian company founded in 2017 that facilitates the data-to-discovery process by focusing on cutting-edge approaches from AI and data science. Particularly, the company provides solutions that address all aspects of the data life cycle, including data storage, data stewardship, data and knowledge representation, machine learning and visualization. Practical applications of these technologies range from healthcare to brain medicine.

Artificial intelligence may be in any case highly impactful in the attempt to overcome limitations inherent to conventional computer-aided diagnosis. In fact, investigators have already created programs that simulate expert human reasoning in clinical decisions. Hopes that such a strategy would lead to clinically useful programs have not been fulfilled, but many of the problems impeding creation of effective artificial intelligence programs have been solved. Strategies have been developed to limit the number of hypotheses that a program must consider and to incorporate pathophysiologic reasoning. The latter permits a program to analyze cases in which one disorder influences the presentation of another. Prototypes embodying such reasoning can explain their conclusions in medical terms that can be reviewed by the user.

The application of AI for diagnosis with medical imaging is also a very dynamic area on which many start-ups compete. Medical and clinical imaging demand, in general, keeps increasing at a pace that overwhelms existing healthcare systems, and makes disease diagnosis much more difficult. AI offers the opportunity to better address these issues, specifically in the neuroimaging field. Precission medicine seems to be bringing an exciting new era in patient care, by enabling the tailoring of treatments to change and improve clinical outcomes. Start-ups are working to improve patient care by placing the most advanced AI tech for neuroimaging in the hands of, basically, radiologists and neuro-clinicians. On their missions we can find ambitions to provide universal and timely diagnosis to enable life-saving treatments worldwide.

These technologies can indeed empower doctors to release fast data analytics, make better treatment decisions for patients in hospitals, and strive for excellence in medical expertise with proprietary algorithms, data analytics and neural networks. Benefits for patients range from shorter time between examination and scan description to early alerts that offer detailed auto-detection of pathological changes. These technologies are nowadays starting to equip radiologist with advanced visualization, quantification, and comparison methods of existing data. Physicians have therefore access to different suites of artificial intelligence tools, which are integrated into their work environment to optimize patient care and enabling predictive and personalized medicine.

Artificial intelligence tools are also being embedded in intensive care units. Intensive Care Medicine is the heart and critical component of hospitals, accounting for around 20-25% of hospital resources. Many of the surgical and non-surgical advances within the last four decades are rooted and closely connected to the development of Intensive Care Medicine (Carson et al, 1996). Providing high-quality intensive care protects and ensures not only patients´ own life survival but also the quality of that life. The ageing European society and the emergence of healthcare crises, such as the 2020 coronavirus pandemic, are leading to a drastically increased demand for intensive care beds worldwide. Today, only 47% of hospitals have the recommended coverage of intensive care specialists, and they are unevenly distributed between centers and peripheries. The demand for Intensive Care Medicine is expected to double by 2030. The quality of care highly impacts the cost burden on global healthcare systems and economy in general (Halpern and Pastores, 2015). The drastically increased data density may eventually lead to an increased amount of treatment errors. In this context, telemedicine has emerged as a key technology to bring high-level medical care to patients. Long ago multiple studies had already shown that providing a dedicated intensivist at an ICU leads to a significant reduction in mortality and reduces the length of stay (Reynolds et al, 1988).

To address this problem, the start-up **CLINOMIC** has created "*Mona*", the first integrated hardware-software platform specialized for the intensive care domain. With a patient-centric view, the company creates groundbreaking solutions for critical ills (brain diseases and others) by combining translational medical research, data science and computational intelligence. Mona´s hardware terminal is equipped with state-of the art technology, such as a 5G Module, radar sensors and artificial intelligence chips from NVIDIA. The system is independent from the hospital's infrastructure and enables highly encrypted telemedicine, even when network connectivity is not optimal. In addition, eight microphones enable a loud and clear sound, even in noisy environments.

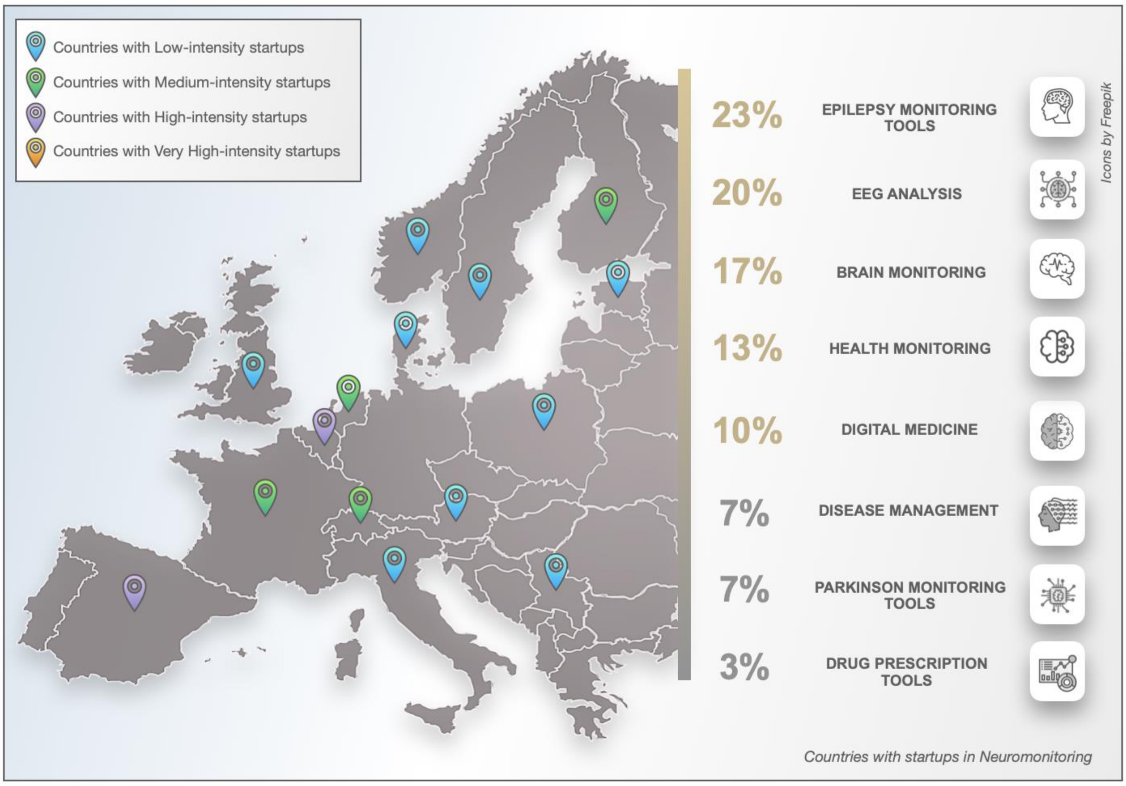
In the battle against Alzheimer Artificial intelligence is also playing an important role. AD is the most common cause of dementia, ranging from 60% to 80% of cases (Domenech and Artigas, 2015). The hallmark pathologies of Alzheimer's disease are the accumulation of the protein fragment beta-amyloid (plaques) outside neurons in the brain and twisted strands of the protein tau (tangles) inside neurons. These changes are accompanied by the death of neurons and damage to brain tissue. Alzheimer's is a slowly progressive brain disease that begins many years before symptoms emerge. Start-ups in the area fundamentally try to use breakthrough AI technologies to change the way dementia is identified and assessed. With the aim of raising patients´ hopes, they offer clinicians and pharmaceutical firms higher levels of certainty in Alzheimer's disease diagnosis at the earliest stages. Solutions created by these companies are committed to provide services like early diagnosis, disease prediction, and progression tracking.

OXFORD BRAIN DIAGNOSTICS, a British company, has created Cortical Disarray Measurement (CDM), which is a platform technology designed to assess Alzheimer's disease at the cellular level, in contrast to simple volumetric methods. By extracting measurements directly from standard MRI/DTI data, their solution provides an index linked to the micro-anatomical health of the patient´s brain. Furthermore, CDM software device aspires to offer unique insights into the point at which the disease materializes in the anatomy of the brain and can also identify the location and pattern of change in grey matter quality so that to pursue new levels of diagnostic certainty beyond simple measures of quantity.

3.3. NEUROMONITORING

For more than a decade, the need to measure brain functions in real time has become a key objective in medical teams, which seek to have effective application in the intraoperative and intensive care phase, also in conditions such as brain injuries or stroke (Keller et al, 2011). These innovation concerns have been a spill over factor to the industry, which is shaping innovative projects in the neuromonitoring sector. The Swiss start-up **LUCIOLE MEDICAL**, for example, combines Near Infrared light with AI algorithms that identify oxygenation levels through signals received from the brain and heart in their own manufactured devices. The ability of technological leaders to create and patent even-smaller systems, with flexible materials - being marketed on the same platform or with interconnected devices – and offer integrated applications with accurate and real time data of brain activity will accelerate competitiveness in the sector and ensure the loyalty of its users. Countries with higher activity in this area are described in fig. 13

Figure 13. Start-ups intensity in the Neuromonitoring area



A large proportion of these projects are working hard to increase the current benefits of neuromonitoring by moving efforts also to areas as attention, memory, learning or other cognitive functions, which are in most cases severely affected by brain diseases. We must note that, as these products normally require to be used by the individual for prolonged periods, such as the EEG devices used during sleep to record and decipher the signals of the brain, the innovators in the field have to invest an important range of resources in R&D so that to optimize their designs and maintain the reliability of their results. A remarkable example of that is given by the Spanish start-up **SCIGNALS**. Efforts are made in equipment that not only seeks to create solutions at a non-invasive level, but also anatomical and comfortable models for the user, motivating their continuity for prolonged and repeated use.

New start-ups in this area are also launching products with satisfactory results in the mental health field, combining new devices that record brain activity, such as EEG, with internet through headphones designed with less invasive and comfortable materials for continuous use, e.g. the Swiss start-up **IDUN Technologies Ltd**. This a group of start-ups whose main objective is to decipher the information received from users, about their emotional states, and allow their connectivity with other digital devices, adapting these applications to achieve a personalized experience. They also offer the possibility of applying the solutions to multiple areas beyond neuroscience, such as gaming, consumer testing, marketing, or mindfulness. As companies with a high capacity for innovation, wide scope, and originality, they have managed to capture the attention of big players such as Microsoft, as well as gaining significant financial support in programs such as Horizon 2020.

On the other hand, although current technologies that record brain activity in pre- and post-surgical processes in elderly patients are widely known by the medical community, those star-ups capable of combining traditional monitoring methods with other key indicators for neurosurgery users have clear possibilities of success. For example, start-ups such as **BRAINDEX**, explain in their main publications some of the limitations that current technologies find in its field, focused mostly on EEG or brain oximetry, and solutions are not found in a single method or device, but the combination of specific indicators (Schraag, 2019). Among other arguments, they encourage the development of new solutions that combine measures that record brain activity during the intraoperative phase -such as EEG, cerebral oximetry to mention some- with other technologies such as, for example, machine learning algorithms. It is still complex for experts to confirm the definitive state of brain function or unconsciousness in the period of anesthesia, which is an aspect that, together with the possible influence on the postoperative recovery of the patient, constitutes an opportunity for innovation in the sector.

The diverse areas that neuromonitoring embraces also include the well-known brain-machine interfaces (BMIs), which enhance the potential of solutions by combining technologies with state-of-the-art chips and applications in human stem cells, nanotechnologies or brain degeneration. Start-ups such as the Austrian **NORGANOID** seeks with these models to evaluate the effectiveness in drug development in its early stages by reducing the use of animals for experiments and also using AI algorithms, offering innovative solutions with 3D tissues engineered from stem cells or other novel techniques such as organs-on-chips[17]. These solutions favor the recording and monitoring of critical conditions such as Parkinson's or Alzheimer's Disease, while other projects in this field combine non-invasive devices applied to other parts of the body such as arms and wrists to measure muscle activity associated with these diseases, being an interesting example the Danish **PARAGIT**.

The variety of neuromonitoring technologies offered in the European market stand out for providing greater control to patients on the registration and management of their own information to be shared with their treating physicians, increasing confidence in the use of these solutions, and attracting new investors to support health monitoring platforms. The growing possibilities allowed by the analysis of data for a personalized medicine facilitate optimal R&D processes for the creation of better medicines, which combine the advances of AI and the expertise of medical researchers. Some of these projects include wearables that record brain activity in conditions such as epilepsy, or those of minimal invasion, which with discreet in its presentation, use key measures as the EEG, the ECG from the heart, or those related with muscle activity, for timely care in seizures and also trying to avoid sudden unexpected death in epilepsy (SUDEP). Other projects are developing these devices by adding photoplethysmography (PPG), electromyography (EMG), electrocardiography (EKG), or electrodermal activity (EDA) functions (Brinkmann et al, 2021).

3.4. NEUROIMAGING

This section will describe our findings after the exploration of technologic innovations developed by European start-ups in the neuroimaging area. We can distinct three challenges within the neuroimaging sector: 1) develop technologies that will allow faster and more accurate disease diagnosis, b) make medical imaging more accessible, in general, to the medical community and 3) build data platforms that enable medical staff to acquire software solutions in an easier and efficient way. Countries with higher activity in this area are described in fig. 14.

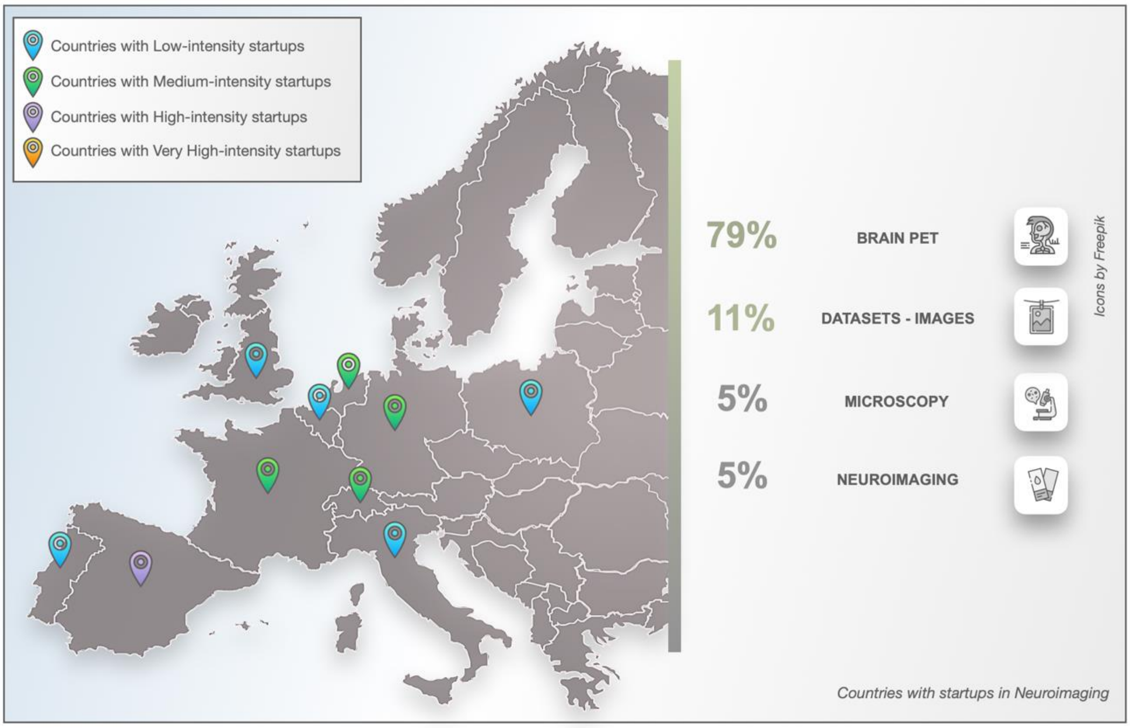
An integrated neuroimaging framework of dynamic and collaborating firms in the area would facilitate the elaboration of a solid strategy for the use of imaging techniques in refining the diagnosis and treatment of brain disorders. Particularly, it would serve to improve diagnostic and therapeutic effectiveness in different neuro-clinical fields, specifically in terms of combined potential to address early diagnosis, monitoring disease progression, predicting treatment responses, and evaluating novel therapeutic interventions. We have classified the start-ups into

17 The Organs-on-Chips are crystal clear, flexible polymers about the size of a computer memory stick that contain hollow channels fabricated using computer microchip manufacturing techniques. Wyss Institute. (https://wyss.harvard.edu/technology/human-organs-on-chips/)

four main categories: those focusing on a various range of purposes under the broad category of “Imaging services”, “Images Datasets”, “Microscopy”, and “Brain Positron Emission Tomography”.

Regarding Imaging services, we have identified several companies delivering a wide range of solutions in the market. There is an interesting portfolio of solutions to assist neurological healthcare. By creating new tools to enable access to the increasing volume of complex information stored in medical images, some European companies are actually contributing to achieve earlier diagnosis, more accurate clinical outcomes, and personalised healthcare.

Figure 14. Start-ups intensity in the Neuroimaging area



In this respect, it is worth mentioning **ICOMETRIX**, a fast-growing company offering innovative AI software for medical image analysis to neurologists, radiologists, and scientists all over the world. They offer a wide range of products: *icobrain ms report* for MRI, objectively assesses lesion dissemination in space and time and provides precise and relevant brain volume change metrics, *icobrain dm report* for MRI which uncovers abnormality patterns in an innovative way, *icobrain tbi for CT* which uncovers mass effects, *icobrain cva* that allows the quantitative assessment of tissue perfusion and finally the *icovid project* which is the continuation of the Belgian icovid initiative and has resulted in the development of *icolung*, a lung imaging AI solution. Co-funded by the EU Horizon 2020 program, the project has grown into a European project aiming to further develop and roll out *icolung* into 800 European centers.

Similarly, the company **MEDIAIRE** has created an efficient solution for quantitative neuroimaging that, integrated into the client's local IT system, generates a report and analysis. Their technology covers brain volumetry, lesion and tumour characterization and aneurysm detection, thus offering radiologists and neurologists a precise, fast and thus efficient solution for quantitative neuroimaging. The Portuguese company **B2QUANT** has also developed a technology called *FLAIR Hyperintensities Quantification*, which can be applied in lesion load analysis in Multiple Sclerosis, and it has also been tested in Traumatic Brain Injury datasets. They have also created *Global Brain Atrophy*, which is mostly used in multiple sclerosis research, and is particularly useful to analyse the progressive course. Furthermore, this technology when integrated in *QuantEmTool* (QET) provides an overall overview of the brain atrophy. The Local Atrophy technology is also available and primarily used to characterise patients with suspected dementia, with current tests ongoing in the domain of Multiple Sclerosis research. The tool has also the potential to assist in the diagnosis of other diseases and conditions like epilepsy and Mesial Temporal Sclerosis.

With respect to Images Datasets, we need to have in mind that neuroimaging experiments usually result in a very complex and varied volume of data, and such data need to be treated and managed in multiple and different ways. In fact, there is not yet a clear consensus on how to organize and share this sort of data. For example, with the *Brain Imaging Data Structure* (BIDS), a German company, **AIGORA**, offers a simple and easy way to organize neuroimaging and behavioural data. The company makes high quality medical image datasets accessible to Artificial Intelligence researchers and developers. Not only the development of robust AI-powered decision support systems requires large amounts of data from various sources, but also getting data ready for AI and making it accessible to researchers is costly and therefore often viewed as a non-core issue by healthcare service providers. The aim is to help making medical image data accessible without compromising data protection and patient confidentiality. The company helps providing access to labelled data from multiple sources covering diverse patient populations, clinical settings, and devices. Potential beneficiaries range from medical imaging centres to pathology labs and medical clinics.

When exploring the area of Microscopy technologies, which are essential sources of these data, you can realise that magnetic resonance imaging, positron emission tomography, and optical imaging have emerged as key tools to understand brain function and neurological disorders in preclinical mouse models. What remained unsolved until recently was the generation of whole-brain microscopy data which can be correlated to the 3D neuroimaging data. Companies addressing this problem are already providing technologies to democratize the scientific use of light field technology with affordable and high 3D performance products.

The Spanish company **DOITPLENOPTIC**, for instance, has created the first plenoptic eyepiece in the market: the *DOIT 3D Micro* is a small and manageable device that converts any conventional microscope into a 3D digital imaging microscope when coupled to the ocular port. Their plenoptic field technology allows to capture image scene from different perspectives to obtain 3D information. Also, it can be applied to display real 3D images on a screen. This technology allows to provide smart products for clinical, biological, and industrial applications, and can be exploited by the entire spectrum of the medical community. In the same direction, **CONFOCAL**, a Dutch company, has developed user-friendly upgrade technologies for microscopes. Their solution, *Re-scan Confocal Microscopy* (RCM), is a super-resolution technique based on a standard confocal extended with an optical re-scanning unit that projects the image directly on a CCD or sCMOS camera.

The quantum efficiency of RCM increases up to 95% in the visible range of light (VIS) and 67% in near-infrared (NIR) light. With this process, RCM achieves 170nm in the RAW image, which can be further improved to 120nm, using easy-to-use deconvolution software. Analogously to the work made by Doitplenoptic, the confocal sectioning can capture multiple 2D images at different depths to reconstruct a three-dimensional structure within the same object or sample. The company offers two solutions, called RCM1 and RCM2, respectively.

We will finalise this section by analysing the activities of the start-ups around PET technologies. The ability of PET is to not only provide spatial localization of metabolic changes but also to accurately and consistently quantify their distribution proved valuable for applications in the clinical setting. PET has clinical value when it can contribute to differential diagnosis, enable earlier diagnosis, monitor therapeutic efficacy, and/or alter clinical management. Furthermore, PET can be used clinically to assist in differentiating types of primary neurodegenerative disorders. These conditions affect more than half of individuals greater than 85 years of age and approximately 14% of individuals greater than 65 years. The most prevalent ones are major neurocognitive disorders due to Alzheimer's disease (AD, 50%–60%), major neurocognitive disorders due to frontotemporal lobar degeneration (FTD, 15%–25%), and major neurocognitive disorders with Lewy bodies (DLB, 15%–25%) (Pujol and Azpiazu, 2015).

In this area, **POSITRIGO**, a Switzerland based company born in 2018 focuses on early dementia diagnosis. Using their brain Positron Emission Tomography system *NeuroLF*, the company intends to develop a device allowing functional brain imaging to everyone at a fraction of today's cost. Their BPET prototype developed at ETH Zurich the company strives for the certification of its imaging system as a medical device under CE and FDA regulations and enter the market by 2022/23. Although the company is still waiting for CE mark and FDA approval, their technology could be exploited by neurologists and neuropsychiatric doctors to better diagnose early stages of dementia on patients.

3.5. NEUROSTIMULATION

Neurostimulation techniques in Europe have shown a strong dynamism in the search for less invasive and personalized methods for the treatment of neurological diseases, which until a decade ago involved approximate global cost of US$ 2.5 trillion and is estimated to become about US$ 6 trillion by 2030[18]. Starting with the well-known challenges facing humanity today, given the rise of neurodegenerative diseases associated with aging, as well as the resources that the health system must face to meet the needs of the growing world population, it is urgent to complete versatile solutions to these demands that are effective in their approach and have a wider reach to end-users. In this sense, some of the fundamental challenges in neurology that have driven the growth and dynamism of these innovations, are related to limited effectiveness in treatments largely due to the well-known blood-brain barrier that hinders the effective absorption of drugs for certain conditions, to reduce the adverse effects of treatments or to be able to prevent their effectiveness from being neutralized due to the advance of these conditions. Factors that together raise the need to find methods that facilitate accurate diagnoses to the medical service, more efficient in the current demands of their routines and significantly complement the studies of specialized researchers. To explain the current trends in this segment they are grouped in a practical way as follows: neurostimulation, bioelectronic medicine, deep brain stimulation (DBS), electrical stimulation, epilepsy diagnosis and monitoring, epilepsy surgery, implants, neuromodulation, neural interfaces and neuroprosthesis. Countries with higher activity in this area are described in fig. 15.

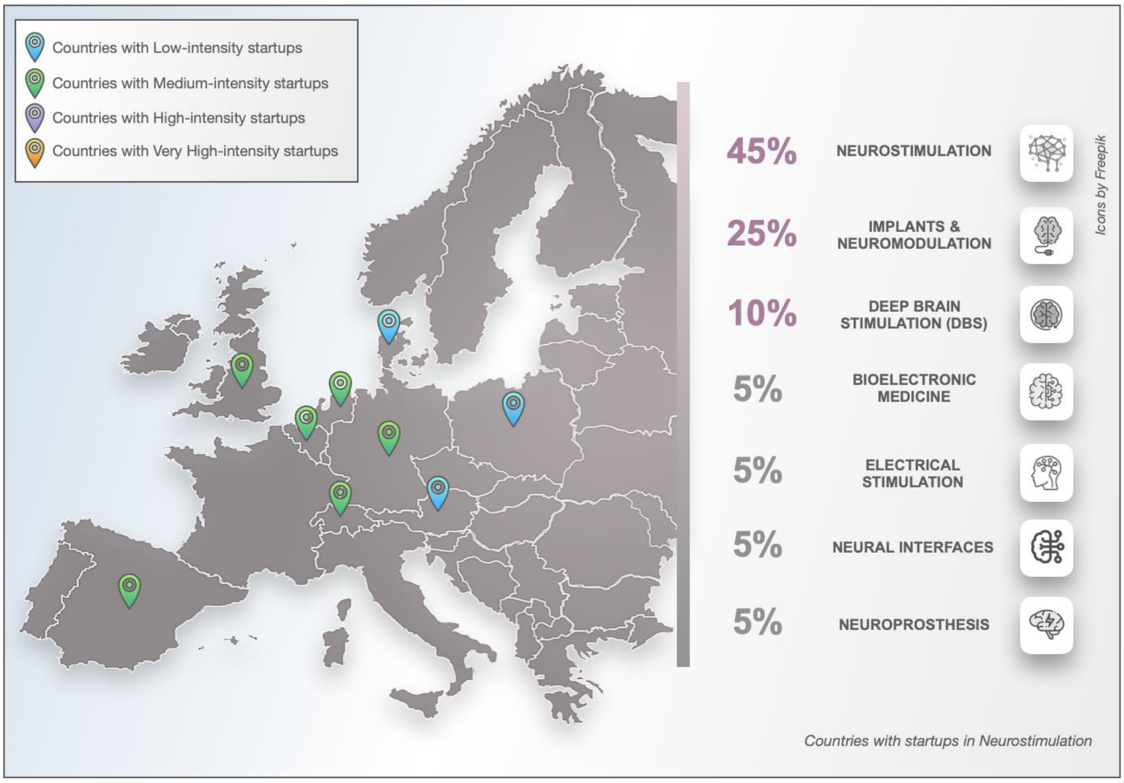
In the field of neurostimulation, European start-ups stand out in increasingly less invasive methods such as Transcranial Static Magnetic Field Stimulation (tSMS) wireless devices or transcranial electrical stimulation (tES) some of which hope to complete clinical trials in the coming years, in patients with Amyotrophic Lateral Sclerosis (ALS) or Essential Tremor, such as the Spanish company **NEUREK**. It also highlights the adaptability of these technologies with limited mobility, with disabilities or in critical confinement situations as the most recent by the COVID-19, which is not only an advantage for those affected, but also a facility for doctors and researchers to have comprehensive applications, to acquire and analyze a large amount of data in real time.

Other start-ups, such as the British **NEUROVALENS,** offer interesting portable EEG systems activating specific regions of the brain such as brainstem neurons, through

18 Neurological disorders are expected to accelerate from 95 million globally in 2015 to 103 million by 2030. (Mishra, 2021) (https://www.proquest.com/openview/31fc23868839899973056b3a31517c70/1?pq-origsite=gscholar&cbl=51651)

effective therapies in conditions such as depression, anxiety, obesity, diabetes, or sleep disorders, gaining the attention of government programs of flagships in the UK to grow and gain visibility. Other non-invasive techniques in the sector are stimulations with gamma waves at 40 Hz in portable devices offering alternative therapies that reveal advances in conditions such as anxiety, depression or memory disorders such as the Danish start-up **OPTOCEUTICS**. Likewise, methods with electrical stimulation to combat migraine are beginning to stand out in a market that has been little served by non-invasive technologies, because many of the projects in the sector are waiting for FDA approval to be commercialized, as commented specialists of this condition and representatives of the start-up **SALVIA BIOELECTRONICS**[19].

Figure 15. Start-ups intensity in the Neurostimulation area



In terms of minimally invasive technologies within this segment, solutions with flexible material implants that modulate areas composed of neurons responsible for the proper functioning of organs affected by chronic diseases stand out, such as **GALVANI BIOELECTRONICS**. Start-ups specialized in the field of epilepsy also excel in new techniques for surgical interventions with expandable electrodes, soon to be introduced in the market, or those innovations that seek to help blind people recover part of the visual functions by the nerve damaged with microchips such as **PHOSPHOENIX**. Other competitive advantages are also reflected in the sample of

19 Press Release. Salvia Bioelectronics (https://www.salvianeuro.com/assets/press_release_salvia_november-3-2020.pdf)

selected companies in neuromodulation, for example, 27% are minimally invasive technologies while the rest offer wireless devices, so the search for lower-risk therapies remains a priority factor in these markets. Likewise, almost half of these start-ups 47% have patented technologies for these techniques and 17% of them are waiting for certificates to be commercialized or are in the early stages of clinical trials.

3.6. NEW DIAGNOSIS METHODS

Early diagnosis is crucial for understanding the evolution of diseases. The start-ups analysed in this area create leading edge technologies addressing the initial development of neurological diseases.

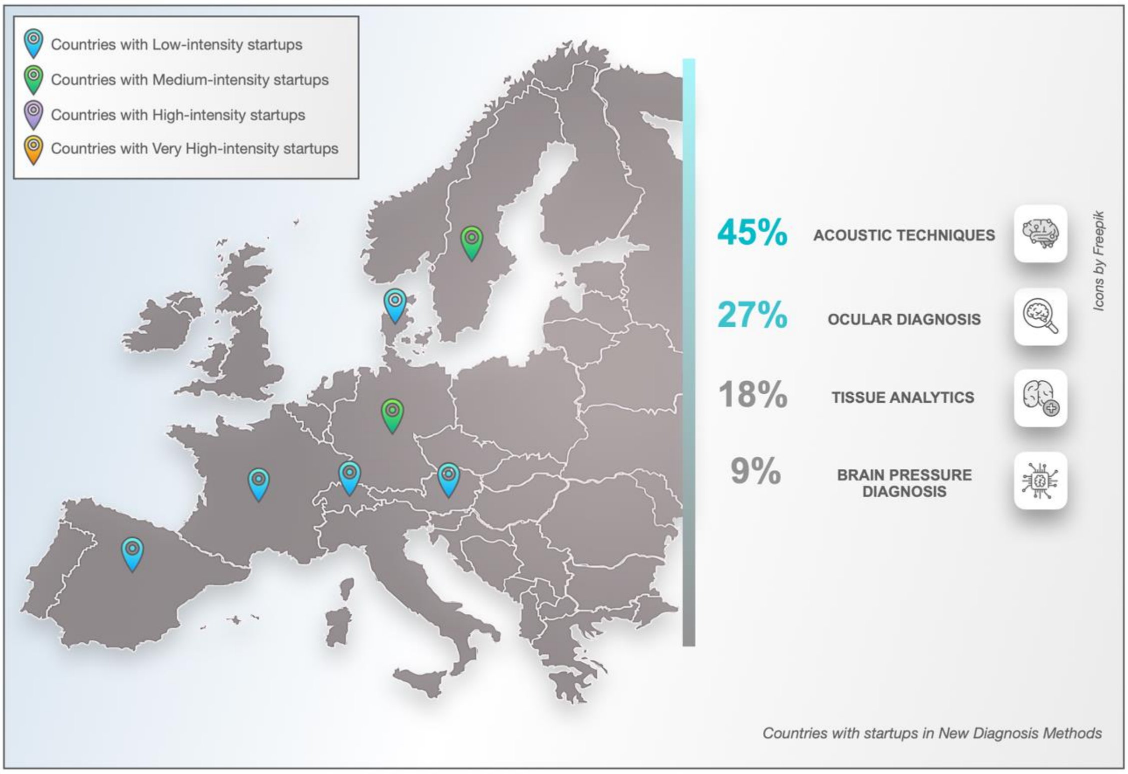
One example of the importance of early detection is found in Intracranial Pressure (ICP), which is a complication of a brain injury, and can result in spatial compression, distortion of compartments, and reduced cerebral perfusion pressure. Several neurological conditions are associated with raised intracranial pressure. When left untreated, ICP can lead to cerebral ischaemia, brain herniation, and death. Invasive monitoring is the reference standard for measuring ICP, as sustained values of ICP have been associated with worse outcomes following traumatic brain injury, subarachnoid haemorrhage, intracerebral haemorrhage, among other conditions. An early assessment of internal damages and increasing in the Intracranial Pressure is crucial to decide an immediate patient treatment, which can eventually ensure successful rehabilitation and minimize functional and cognitive disabilities.

Today ICP is measured in an invasive way by inserting a pressure sensor through a cranial aperture. The invasive procedure is performed by highly specialized personnel and carries along a high cost and risk of infection and bleeding. In this regard, **STATUMANU ICP** is developing *Vesseltrack*, a device that measures and monitors, non-invasively, changes in the intracranial pressure in patients with abnormal and traumatic brain conditions, providing support to patient assessment, clinical decisions, and follow-up treatment of patients. The device combines image technology, precise and advanced optics, proprietary artificial intelligence, and deep learning algorithms.

Instrumental eye movement analysis can be also useful in clinical setting: this technique provides physicians with accurate measures of the different eye movements (e.g., saccades, nystagmus, smooth pursuit, vestibulo-ocular reflex) and related parameters (gain, velocity, accuracy, phase) that cannot be estimated by simple clinical examination. Data acquired through instrumental eye movement examination can be analysed by new data mining and artificial intelligence techniques to increase our ability to discriminate precisely between different neurological diseases. Because eye's retina is the only part of the brain that can be seen directly, this sort of technologies allows physicians and researchers directly assess changes in the brain caused by neurological diseases. A full range of diseases could be diagnosed through ocular diagnosis, including ADHD, Parkinson, vertigo, Alzheimer, ataxia, etc.

The companies analysed under this label, e.g., the German **NOCTURNE**, combine eye-tracking technologies with built-in artificial intelligence models, and have thus created, reliable, non-invasive, and innovative diagnostic methods. By combining complex image processing methods with mathematical 3D modeling, solutions such as 3D morphometry, compute quantifiable parameters for the smallest disease-related changes in the retina's shape. Countries with higher activity in this area are described in fig. 16.

Figure 16. Start-ups intensity in the New Diagnosis-Methods area



New diagnosis methods are also evolving in the acoustic technology area. Up to now, acoustic technologies have basically facilitated transdermal drug delivery, localized drug delivery, and have even achieved temporary disruption of the blood-brain barrier facilitating drug delivery to the brain. Ultrasound technologies have also been used to help dissolve blood clots, remove unwanted fatty tissue, and to heal wounds and fractured bones.

The echo principle forms the basis of all common ultrasound techniques. The distance between the transducer and the reflector or scatterer in the tissue is measured by the time between the emission of a pulse and reception of its echo. Additionally, the intensity of the echo can be measured. With Doppler techniques, comparison of the Doppler shift of the echo with the emitted frequency gives information about any movement of the reflector. Doppler sonography plays an important role in medicine. Sonography can be enhanced with Doppler measurements, which employ the effect to assess whether structures (usually blood) are moving towards or away from the probe, and its relative velocity. By calculating the frequency shift of a particular sample volume, for example a jet of blood flow over a heart valve, its speed and direction can be determined and visualized. This is particularly useful in cardiovascular studies and essential in many areas such as determining reverse blood flow in the liver vasculature in portal hypertension.

CIMON MEDICAL is a company that develops and manufactures novel Doppler ultrasound technology for healthcare. Their technology enables continuous monitoring of blood-flow using non-invasive Doppler ultrasound technology. They have created an innovative solution for monitoring blood-flow in the brain and its main field of application is the medical monitoring of premature or critically ill babies. **NISONIC** is another example of a start-up that has developed a technology enabling non-invasive detection of increased intracranial pressure with ultrasound technology. The ultrasound system consists of a dedicated probe for transorbital ultrasound imaging together with advanced machine learning algorithms for automatic measurements and guiding.

The future will certainly bring many more therapeutic ultrasound techniques to the market and enable better diagnosis as there are a growing number of potential applications of ultrasound energy, ranging from tumour ablation using High Intensity Focused Ultrasound (HIFU) to the stimulation of encapsulated systemic drugs. In this line and as an example, the start-up **SENSPD** is working on an innovative way of detecting autism at a very early developmental stage, based on a physiological marker. By using otoacoustic emission (OAE) their devices measure the sensory perception system performance to detect this brain disorder.

The analysis of tissues also constitutes a promising technology field of brain innovation. Some start-ups are developing novel medical procedures to get samples of inaccessible brain regions. **MEDIMPRINT**, for instance, combines local silicon know-how and health technologies in the design of devices like *Protool*, which is a surgical stylet incorporating a mesoporous silicon surface to collect tissue imprints of the order of 0.02mm, by quick (one-minute) and simple contact with the brain. Unlike the tissue sectioning performed on biopsies, the tissue imprint relies on non-lesional adsorption of brain tissue to the silicon surface, making the peritumoral regions in the various brain cancers accessible for clinical analyses. This innovative non-invasive solution is beneficial for clinical research in brain tumours and neurodegenerative diseases and enables earlier diagnosis.

3.7. BIOMARKERS

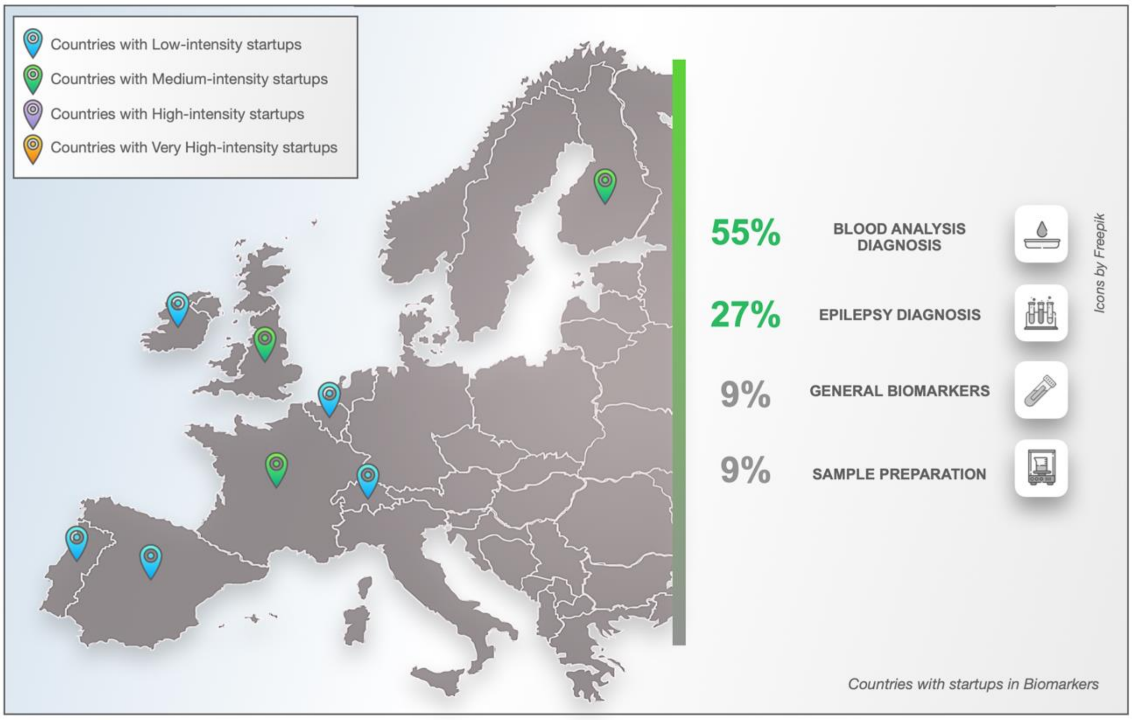
The use of biomarkers in basic and clinical research as well as in clinical practice has become so a commonplace that their presence as primary endpoints in clinical trials is now accepted almost without question. The term "biomarker" refers to a broad subcategory of medical signs – that is, objective indications of medical state observed from outside the patient – which can be measured accurately and reproducibly. Medical signs stand in contrast to medical symptoms, which are limited to those indications of health or illness perceived by patients themselves. The use of biomarkers, and in particular laboratory-measured biomarkers, in clinical research is somewhat newer, and the best approaches to this practice are still being developed and refined. The key issue at hand is determining the relationship between any given measurable biomarker and relevant clinical endpoints. The start-ups analysed in this technology area are creating and developing leading edge technologies focusing on innovative ways of using biomarkers as medical tools. Countries with higher activity in this area are described in fig. 17.

Start-ups in the sector explore, both biomedically and pharmaceutically, human proteoforms from tissue and liquid biopsies in search of innovative biomarkers, readily translatable into drug development applications and/or into novel diagnostics. By identifying tissue and cell specific human secretory proteoforms, they assemble the so called human peptide 'dictionary', and by identifying disease (and health) specific human proteoform profiles, they can record the human tissue 'vocabulary'. This information will be used for the benefit of the patient on clinical fields. The companies we have identified are mainly dedicated to improving the diagnosis, treatment and prevention of acute neurodegenerative conditions.

In this context, **PROTEOFORMIX**, a Belgian enterprise, is running a top-down proteomics-based translational biomarker discovery platform. They employ state-of-the-art and proprietary technology to identify disease-associated proteoforms (e.g., peptides) in clinically sampled human tissues and biofluids. They also run modern mass spectrometry, which holds significant potential for the discovery and sensitive detection of innovative (sets of) biomarkers allowing rapid and accurate diagnosis of multiple disorders simultaneously in a single patient's small-volume sample. Moreover, biomarkers can be used in the creation of diagnostic kit for the detection and evaluation of brain impairment and brain diseases.

The Finnish **MEDICORTEX** is developing a biomarker diagnostic test for Traumatic Brain Injury (TBI). This test can be used to identify individuals with TBI, who are at risk of secondary brain injury and therefore require increased surveillance, or for those individuals with mild TBI, who otherwise may remain undiagnosed and untreated. A diagnostic test can also be applied in cases where there are no external signs of injury. The TBI diagnostic quick test Medicortex is developing will be the first biomarker from a non-invasive sample of body fluid approved by regulatory agencies for the diagnosis or prognosis of TBI immediately after injury.

Figure 17. Start-ups intensity in the Biomarkers area



There also a set of companies focused on developing test that can measure the levels of biomarkers in patients´ blood. These markers include enzymes, hormones, and proteins. The French start-up **Agent T** is using biomarkers found on blood samples to find the Alzheimer's pattern among billions of potential signals. Using Artificial Intelligence, their multiomics platform is designed to detect Alzheimer's at its earliest stages to help clinicians optimize the next generation of precision therapies. Likewise, a Portuguese company called **ILOF** concentrates its efforts on early stages of Alzheimer disease. Their cloud-based library of optical fingerprints, powered by photonics and AI, provides non-invasive tracking, screening, and stratification for drug discovery, adapted to each clinical trial needs. They also develop a blood-based screening test that stratifies patients for clinical trials, removing heterogeneity due to pathophysiology, disease stage or degree of progression.

Biomarkers on epilepsy is another dynamic field for European start-ups. Epilepsy is a serious neurological condition that affects almost 1% of the population at some period during their lives. It is characterised by the tendency to have recurrent, spontaneous, seizures. Seizures can be caused by several different mechanisms and originate in and propagate to various locations in the brain. **NEURONOSTICS** is a British company focused on developing clinical decision support tools and at home monitoring devices for people with suspected neurological conditions. Their first product, “#*BioEP*” (Biomarker of Epilepsy) is a revolutionary, patented biomarker of the susceptibility to seizures in the human brain, informed by clinical EEG recordings. #*BioEP* works innovatively by transforming short segments of routinely acquired EEG into a mathematical model of the brain. Computer simulations of this model provide a proxy for seizures, rapidly revealing the susceptibility of a subject to seizures and thereby providing an objective indication of epilepsy. In addition, it offers an insight into prognosis by measuring the temporal response to treatment. This is achieved by comparing values of seizure risk measured from EEG recordings prior to and post administration of AEDs.

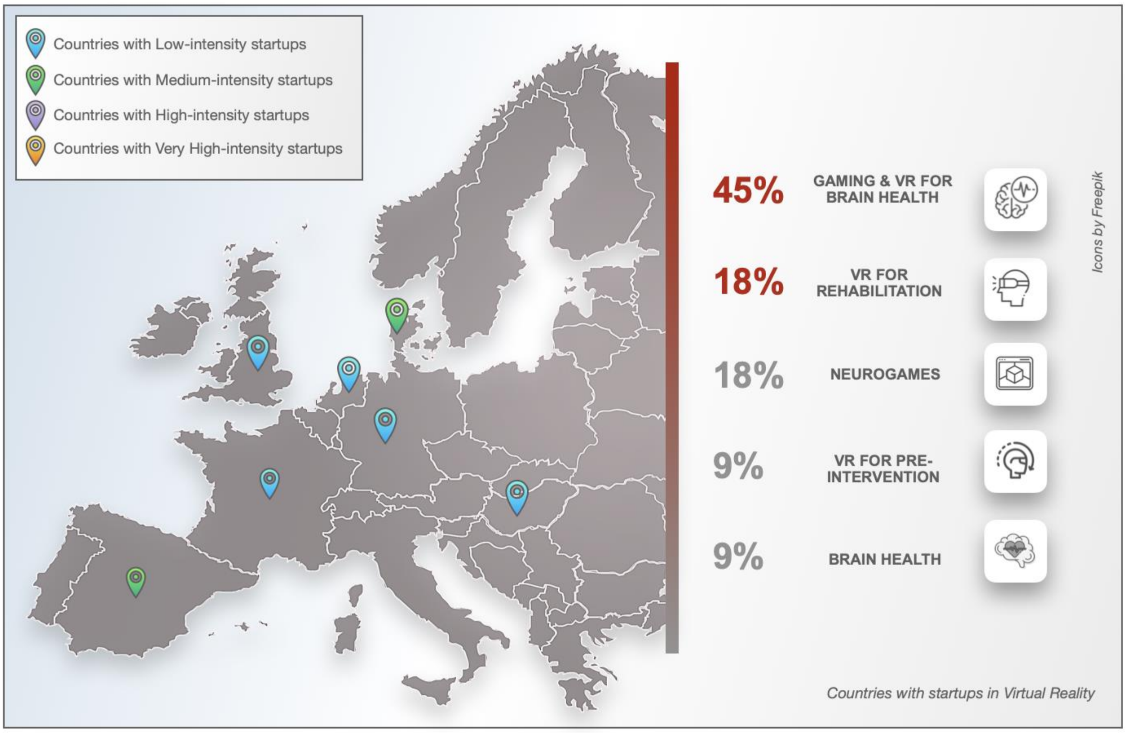
With respect to sample preparation for biomarkers, we can highlight the work of **SCIPIO BIOSCIENCE**, a French company that exploits a proprietary technology that allows the preparation of samples for single-cell profiling. Based on a novel combination of established biochemical and biophysical approaches, the Scipio technology achieves single-cell barcoding in a test tube format. This technology results on a powerful benchtop kit to extract mRNA from single cells. The kits are expected to be commercially available early 2022, and ready for utilisation on any benchtop.

3.8. VIRTUAL REALITY

Virtual reality (VR) is an emerging technology with a variety of potential benefits on multiple aspects of rehabilitation assessment, treatment, and research. Through its capacity to allow the creation and control of dynamic 3-dimensional, ecologically valid stimulus environments within which behavioural responses can be recorded and measured, VR offers clinical assessment and rehabilitation options that are not available with traditional methods. Start-ups in the area operate with both virtual reality technologies and AI in their medical research and development effort. Their scope moves from the utilisation of VR both on rehabilitation and/or pre-intervention to Virtual Reality used for learning purposes. Countries with higher activity in this area are described in fig. 18.

Cognitive rehabilitation is based on the principles of neural plasticity, describing the malleability of our nervous system. Through various internal and external stimuli, new connections can be created in the brain and strengthened by repetition or weakened by disuse. Resulting from these processes whole brain areas can change and adapt to specific needs. **LIVINGBRAIN**, a German start-up has decided to take advantage of this biological principles and has created a technology that stimulate the brain in a way it induces neural plasticity after injuries of the nervous system and helps to bring back lost abilities. The company proves that virtual reality offers several advantages for rehabilitation. On the one hand, it is possible to train potentially dangerous situations repeatedly without actual danger. In addition, while many activities of daily living are difficult to train several times in a row, training these activities is easier with the support of virtual reality. Furthermore, VR is location-independent, given the mobility of available technical devices. Consequently, numerous scientific publications suggest the use of virtual reality for therapy and treatment of various diseases. Their solution, called *teora® mind* is a CE-certified medical device of class 1. It is a medical device compliant with the Medical Device Directive and is intended for training of cognitive impairment and rehabilitation of neurological disorders.

Figure 18. Start-ups intensity in the VR area



In fact, neurobiological effects of virtual reality on neuronal plasticity have been proven to result in increased cortical grey matter volumes, higher concentration of electroencephalographic beta-waves, and enhanced cognitive performance. Clinical application of virtual reality is aided by innovative brain–computer interfaces, which allow direct tapping into the electric activity generated by different brain cortical areas for precise voluntary control of connected robotic devices.

Virtual reality is also valuable to healthy individuals as a narrative medium for redesigning their individual stories in an integrative process of self-improvement and personal development. In this sense, the companies analysed have developed a range of technologies using virtual reality for medical purposes. Implementing science-based neurorehabilitation for effective and functional recovery of motor and cognitive function after brain damage, **EODYNE SYSTEMS** is a Spanish start-up that develops a technology that is tailored to the specific needs of each individual patient, from the acute to the chronic phase after brain damage. Their solution has been validated by neuroscience experts and clinicians in several hospitals and has a Class I Medical device certification.

Furthermore, research shows that virtual reality can reduce acute pain during medical interventions, as it reduces stress and anxiety. It also encourages physical activity and decreases fear of movement. Results have shown that patients receiving a VR intervention have significantly lower postoperative pain scores than those receiving the usual care. In this line of work, the Dutch start-up **SYNCVR** has created a medical platform enabling physicians to implement VR throughout the hospital. The implementation may imply hardware, software installation, workshops, agreements with other supporting services as well as the adoption of hygiene protocols. **HEALTHYMIND** is a French start-up that provides healthcare professionals with an evidence-based medical device that combines immersion through virtual reality technology, medical hypnosis, and advanced therapeutic principles to alleviate pain and anxiety of patients. Their solution, which has been developed in close collaboration with healthcare professionals and neuroscience experts, is built on immersive technology, portraying 3D visual and auditory experience with cutting-edge graphics quality. It integrates clinical hypnotherapy and mature therapeutic principles, such as music therapy and cardiac coherence, that have shown anxiolytic and analgesic benefits while reducing medication consumption and helps in speeding up the patient's recovery reducing the length of hospitalization. Their technology can be used before, during, and/or after an anxiety-provoking or painful procedure, and works on a wide range of medical sectors, such as anaesthesiology, surgery, oncology, palliative care, paediatrics, and radiology.

Virtual reality also facilitates the utilisation of neuro-games whose objective is to assess and reinforce individual´s specific cognitive functions. **BRAIN+** is a Danish company that has created Brain+ Recover, a flexible tool that automatically adapts to each user's unique cognitive needs. The user's cognitive capabilities (attention, executive functions, working memory and episodic memory, and language) are assessed upon the initial session and a tailor-made program is generated based on such assessment. *Brain+ Recover* is a gamified neuro-rehabilitation platform, designed to create an immersive and captivating experience which increases user focus, and generate high adherence rates. Their solution is built on two different pillars: a set of scientifically designed cognitive exercises that stimulate neuroplastic adaptation and recovery (. the unique Brain+ method makes training more personalized, precise, intense, and effective) and the virtual *BrainCoach* which helps user to develop brain-healthy habits and implement them in daily life. The program also includes metacognitive therapy, mindfulness, and other guided exercises.

Finally, we need to mention how VR and AI offer the opportunity to medical students and physicians of improving their medical skills. In this sense, a Hungarian start-up called **INSIMU** provides integrated e-learning services for clinical training programs in healthcare, providing a safe environment for students to improve their clinical reasoning skills. The company offers training programs for Medical, Nursing and Physician Assistant students. Their technology allows students to practice medical diagnosis in the safety of a virtual clinic with an unlimited number of simulated patients and a full range of agnostic methods.

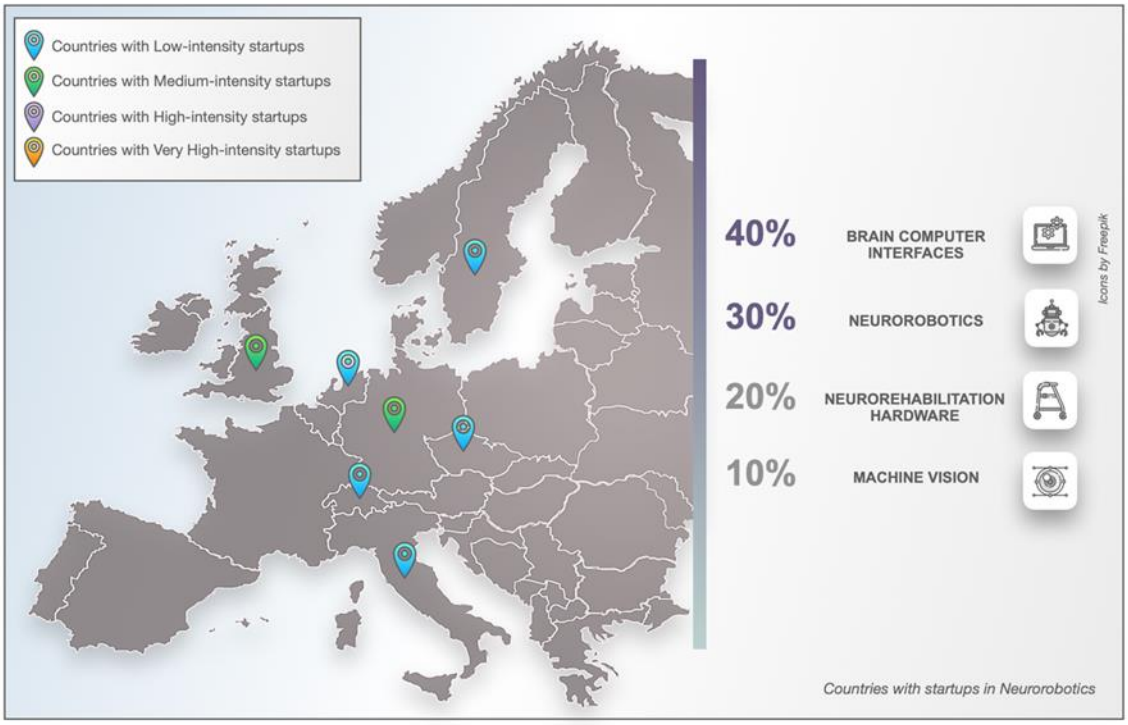
3.9. NEUROROBOTICS

Neurorobotics represents an industrial sector whose technological progress - in fields like neurorehabilitation, brain computer interfaces, or machine vision, to cite only some areas - demonstrate the power of brain innovations and the impact these innovations may have in individuals. Neurorobotics applied to neurorehabilitation, for instance, aims in essence to provide innovative solutions for patients with nervous system issues. Neurological diseases usually reduce the patient's quality of life considerably. In such cases, multimodal physiological data and processing methods can be used to improve the rehabilitation process. Neurorehabilitation technologies seek to take advantage of the functional neuromuscular structures preserved and compensate or re-learn the functions that damaged areas previously made.

The start-up analysed under this section claim that today's modern technology and advanced rehabilitation methods shouldn't be constrained by physical space, time, or resources. Instead, the accessibility to cutting-edge technology should be available to anyone suffering from neurological diseases or cognitive impairment. **BRAIN STIMULATION**, a Swedish company specialized on building solutions enabling to regain, develop, and sustain cognitive and motor function after stroke and acquired brain injuries, has created multiple technologies to improve stroke management. Their first product, *RehAtt® DiSTRO* is a highly accurate digital diagnostics tool that offers recommended cognitive tests and come up with personalized rehabilitation programs under 15 minutes. They have also created *RehAtt® MR*, a rehabilitation tool that provides individualized rehabilitation for cognitive and motor functions in a realistic and stimulating Mixed Reality environment. This technology offers hyper-personalized and effective rehabilitation, and its stimulating enriched 3D game environment increases motivation, independence, and quality of life. Countries with higher activity in this area are described in fig. 19.

Robot therapy, in parallel, could be used for those patients whose degree of functional impairment is too severe, so the robot can help to repeatedly perform the correct exercise. In the rehabilitation paradigm virtual reality technology is considered essential because VR could give various interactive environments, having cognitive factors, which is hard to provide in real situations. In addition, when the patient makes movements as they intended in a well-designed virtual environment, it would activate the motor system network and the cortical reorganization could be augmented in the process of learning to correct errors. Combining VR and robot technology in rehabilitation may therefore have high impacts on the effectiveness in various perspectives, such as a multimodal approach for the gate training of individuals suffering from numerous brain-related conditions.

Figure 19. Start-ups intensity in the Neurorobotics area



In this context, **AUTONOMYO** is a Swiss start-up building technology that enables people with neurological gait disorders to walk again and win back freedom of movement. Gathering a team of engineers, developers, rehabilitation experts and healthcare professionals their aim is to develop a solution which makes a better future for movement impaired people. Originated from an EPFL project, the company provides a robot-based rehabilitation solution to increase accessibility and training intensity for people with neurological conditions. Their product is an exoskeleton that secures the vertical position and guides the motion of the lower limbs, as well as enhances the number of repetitions while performing task specific exercises. The device measures all posture parameters (symmetry, step length, weight transfer) and provides instant feedback to the user. The solution picks up on the patients´ current abilities to detect and provide the required assistance level for optimised training.

From other perspective, we can observe the synergies generated when Robotics and Brain computer interfaces (BCIs) are technologically combined. BCI systems give their users communication and control capabilities that do not depend on muscles. User's intentions are determined from activity recorded by electrodes on the scalp, on the cortical surface, or within the brain. BCIs can thus enable people who are paralyzed by amyotrophic lateral sclerosis, brainstem stroke, or other disorders to convey their needs and wishes to others, to operate word-processing programs or other software, or possibly to control a wheelchair or a neuro-prosthesis.

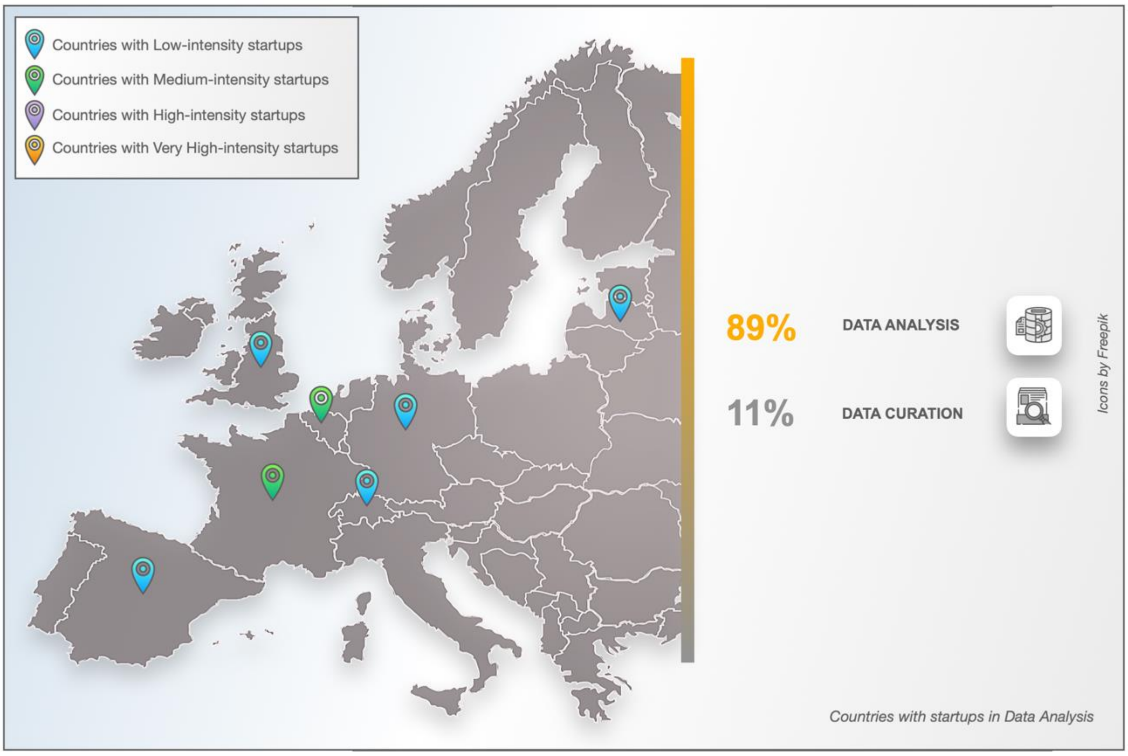
BCI technology might also augment rehabilitation protocols aimed at restoring useful motor function. The companies analysed in this area work to provide patients with neurological disorders or sensory deficits with new opportunities to adapt and improve their condition under their own power, offering solutions that increase patient independence and improves their quality of life. **MINDAFFECT** and **CEREGATE** are two European start-ups that are specialized in the application of artificial intelligence and Neuroscience to enhance human communication. They have created ground-breaking BCI products, giving locked-in patients the ability to interact with the outside world by controlling a computer solely with brain signals. Their technology includes the tracking, interpreting and transmitting of a wide range of neuron signals, Both are working with industry leaders to create exciting new applications in next-generation hearing and vision testing, brain health monitoring and neural communication.

BIORETICS, an Italian company founded in 2012, work on biologically inspired methods embedded into well-founded theoretical frameworks. Focused on R&D in Machine vision based on Machine Learning, they have created technologies that seem more reliable, fast, and cheap than human beings in decision processes based on vision. BIORETICS today serves as industrial partner for high quality AI-first projects where 2D/3D imaging is the primary data source for extracting high level information. Their focus is mainly devoted to 2D, 2.5D and 3D massive real-time image analysis especially when gathered from heterogeneous sources. All codes are always highly optimized to reduce the environmental impact produced by training and deploying AI models. The company offers multiple solutions, such as the AI-first industrial-grade software framework called *Aliquis*®, used for developing and deploying applications that mimic human vision. *Aliquis*® makes available an abstract machine to interpret and execute real-time workflows and understand massive visual data streams through the declarative and domain-specific Aliquis® programming language.

3.10. DATA ANALYSIS

Currently only 15-25% of data from hospitals is systematically structured. Manual data collection is costly and not realistic when the reviewing of millions medical records is needed. Furthermore, 48% of MedTech companies believe that EU MDR (European Medical Device Regulation) will cost more than 5% of their annual revenue. Most of them even rely yet on simple calculation spreadsheets to capture and process their clinical data. Start-ups in the area are currently developing systems to promote collaboration between biomedical institutions, patient organizations, and research partners, through the identification of biomedical data from metadata files, and the engagement of population cohorts and new patients in medical research. They also offer solutions that allow physicians to use meaningful biological information before deciding on treatments for patients. By analysing EEG/ECG data and biomarkers these solutions help doctors to find effective personalized treatments to neurological diseases. Countries with higher activity in this area are described in fig. 20.

Figure 20. Start-ups intensity in the Data-analysis area



These companies also offer solutions to better plan clinical trials, specially by the stratification of trials´ population according to EEG/ECG biomarkers. This results on the creation of an end-to-end virtual environments for biomedical institutions, patient organizations, and research partners, thus enabling them to communicate directly, and ensuring a safe data curation and compliant, consent-enabled biomedical data utilization for research, clinical treatments, and trials. **DEEPTRIAL**, for example, is a start-up with a monitoring system that seeks to promote the next generation of clinical trials using AI and analytics for a better personalization of these trials. They capture patient's physical and mental health conditions data, as well as a range of hidden outputs within the trial process. The company aims to provide a precise and personalized medicine through an intelligent and multi-modal platform for pharma and medical devices companies, enabling them to develop better drugs and develop optimal health models of the patients.

The start-up **LONGENESIS** offers an interface where anonymized metadata metrics are published, thus allowing potential partners and sponsors to query datasets by the inclusion and/or exclusion of specific criteria, as well as by sending collaboration requests. Metadata files can thus provide a general overview of patient cohorts without releasing externally any patients´ private information. The company has also developed a management tool that ensures the full cycle of consent registration and management. It allows the proactive participation of patients in research studies, as well as a biomedical/clinical data processing, based on the extent and scope of the given consent. The solution is offered as an API to be integrated into already existing interfaces, or as a stand-alone white-label web application.

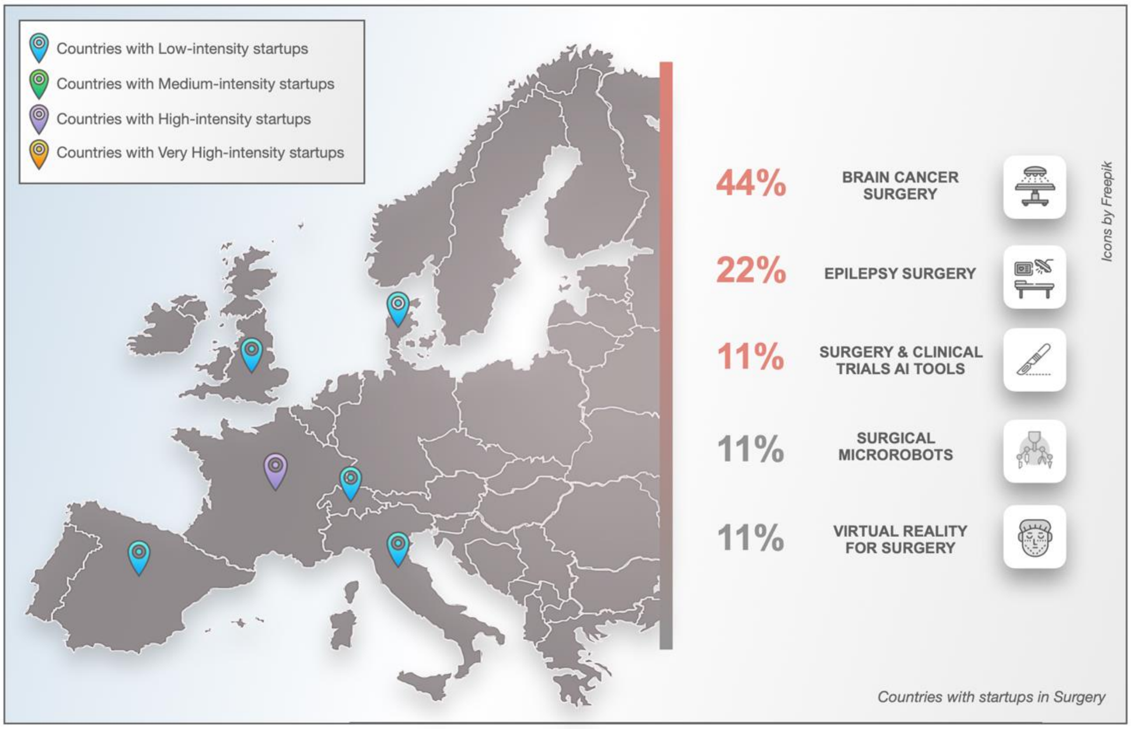
3.11. NEURO-SURGERY

Start-ups in the surgery domain deal with artificial intelligence technology, microrobots and virtual reality in their efforts to improve procedures, trials, and therapeutic effectiveness. The application of these technologies has provided surgery practice with new methods that facilitate the utilisation of large amounts of data for clinical purposes. Countries with higher activity in this area are described in fig. 21.

It is particularly remarkable the need of developing reliable pre-surgical risk assessment tools and prevention measures that help improving patients´ quality of life after surgical interventions. **PREDICTHEON** is a Spanish company that develops algorithms using mathematical models embedded in a software that can be implemented in different platforms, including clinical monitors, infusion pumps, and electronic health records. Their solutions are integrated by a processing system that receives and processes real-time clinical signals from patients, using mathematical models and algorithms that perform predictions. It provides an intuitive display of those predictions, which are continuously updated over time. This technology derives from the use of a powerful data analysis engine based on population analysis, predictive analytics, nonlinear mixed-effects modelling, and data science approaches including artificial Intelligence methods. The use of predictive models generated from patient data provides the clinician with new information that can help to improve clinical decision making.

Likewise, the firm **PIPRA** is helping clinicians to evaluate the risks of neurocognitive complications for patients undergoing surgery and allows the adoption of protective personalized operative measures. Standard medical data are quickly uploaded on the PIPRA user-friendly web or mobile app and accurate results are promptly delivered. This solution can be easily integrated into the current clinical workflow and could improve the overall surgical performance.

Figure 21. Start-ups intensity in the Neuro-surgery area



We would also like to mention the work of **WISE**, a medical device company with a unique technology that allows the production of stretchable and flexible electrodes on medical-grade elastic polymers. WISE's electrodes are highly ergonomic, conformable, soft, and thin, thus allowing great adhesion, minimal invasiveness, and excellent adaptability on neural tissues, addressing major limitations of other existing technologies. They have the potential to improve the performance of neuromonitoring as well as the treatment of patients who are already benefiting from neuromodulation. Presenting a full range of technologies, they have created a CE-marked product called WISE Cortical Strip (WCS®), part of the WISEneuro® Monitoring family, which is composed of platinum electrodes embedded in a soft and thin film of medical grade silicone. It is used for continuous recording of the brain's spontaneous electrical activity (ECoG) and somatosensory evoked potentials (SEPs). It is as well used for brain stimulation, aimed to elicit motor evoked potentials (MEPs). Pre-clinical studies have confirmed the excellent functionality, reliability, safety, and usability of the WISE Cortical Strip for intraoperative neuromonitoring.

Mobile microrobots have also the potential to transform surgery and clinical procedures. Their small size and wireless mobility can enable access to and navigation in confined, small, hard-to-reach, and sensitive inner body sites. Thus, they offer new ways of minimally invasive interventions, targeted diagnosis, and therapy down to the cellular length scales with high precision and repeatability. The exponential and recent progress of the field at the preclinical level anticipates great expectations in the short term. Microrobots have shown significant potential to conduct tasks such as drug delivery, cell manipulation, micro-assembly, and biosensing using manual control. Microrobots could also be used for minimally invasive surgery. Expansion of these capabilities into surgical microrobots would enable more precise targeting of sampling locations.

The companies analysed in the area are focused on micro-robotic surgery instruments that enable higher precision and therapies on brain diseases affecting more than a billion people worldwide. In this context, **ROBEAUTÉ** is a French company that develops microrobot tools for novel therapies in hard-to-reach areas of the body. Designed specifically for the brain, the device can be used by neurosurgeons. Their technology offers a free navigation through complex regions of the body to perform biopsies, collect precise anatomically localized data, and deliver therapies on site.

There is already strong evidence on the impact that virtual reality and robotics will have in health care in the next decade. Clinically validated and powerful medical simulators are now available and ready to be used across the world. While general surgery is leading the utilisation of simulators, and neurosurgery is leading the use of augmented reality and image guided surgery. Robotics are used for accessing parts of the human body that were unreachable. Other virtual reality applications are being used in mental health, anaesthetics, and emergency medicine. Rapid development in the internet and “e-learning” domains have accelerated the dissemination of simulation techniques, interactive 3D images, and structured courseware. A successful medical simulator or surgical system based on virtual reality requires the participation of a team of specialists including experts in ergonomics and applied psychology, software engineering, digital 3D design, electromechanical engineering, robotics, and microtechnology. The crucial factor that will determine the uptake of virtual reality technology by surgeons will be the demonstration that virtual reality systems are able to deliver reliable and valid training and assessment functionalities.

Recent publications suggest that not only has the virtual reality community produced already experimentally validated systems for the training and assessment of surgical skills, but it has been done by using established techniques that are now impacting the market and benefiting the overall surgical performance. In this sense, **AVATAR MEDICAL** creates patient avatars to help surgeons prepare their surgeries. Their technology generates 3D patient representations based on their medical images in an interactive virtual reality context. These 3D avatars are generated in real-time: they can provide an accurate and instantaneous means for clinicians to understand their patient's medical image. AVATAR MEDICAL uses virtual reality and Bayesian approaches to allow ultra-fluid navigation within medical image based patient avatars. Compatible with all tomographic image types, no data pre-treatment is required. As a result, AVATAR MEDICAL´s unique technology allows physicians to adjust patient representations in real-time and within a virtual context.

3.12. GENETICS

Solutions in this field are consolidated in precision medicine, through regenerative therapies that provide protection by modifying the desired genetic information in the face of adverse neurodegenerative conditions such as motor neuron disease[20], as well as infectious diseases. In companies such as Avrion Tx, for example, once the target to intervene has been identified, a genetic component is prepared to be validated in an In Vitro and In Vivo scheme and finally the most effective component in these experiments is selected. There are projects in which once the tissue sample is preserved -in situ sequencing (ISS)[21]- these genes are analyzed from the initial location, commercializing the technique created for these analyses, through customized modules adapted to the demand of researchers and with built-in microscopic systems that allow high spatial resolution, such as CARTANA. In addition, these start-ups are demonstrating that their role in the industry can contribute to other disciplinary fields no less relevant such as oncology or immunology (Hernández et al, 2021).

Other leading experts such as Dr. Carolee Barlow, Chief Medical Officer at ESCAPE Bio, in an interesting podcast for the start-up **SANO GENETICS**[22], explains how these gene therapies are currently applied not only to make correct diagnoses, but also to direct treatments in key areas of the brain and contribute to the rejuvenation process, especially in those conditions in which movement is affected, as in Parkinson's disease. Additionally, she explains that in conjunction with highly specialized laboratories such as Merck, they develop treatments for

20 "Motor neuron disease usually refers to amyotrophic lateral sclerosis" Nature, 2021. [https://www.nature.com/subjects/motor-neuron-disease]

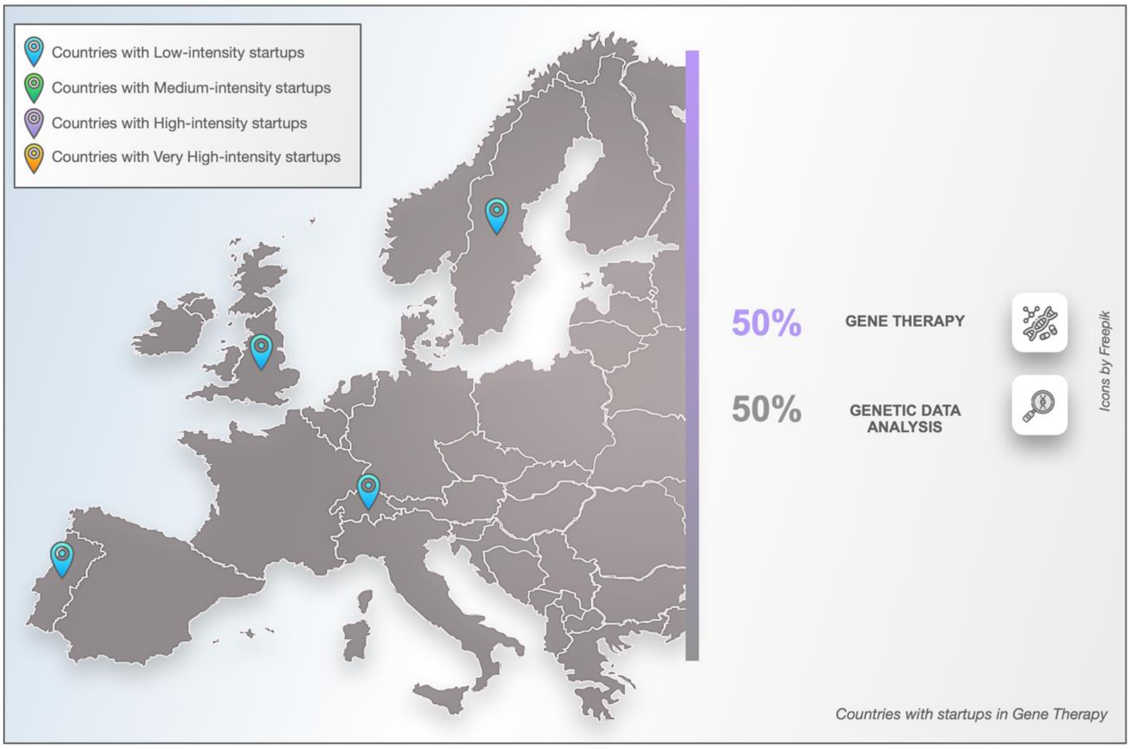
21 "Mapping brain cell types with CARTANA in situ sequencing on the Nikon Ti2-E microscope". (Hernández et al, 2021). [https://www.nature.com/articles/d42473-019-00264-8]

22 Precision Pioneers EP 8: Chief Medical Officer at ESCAPE Bio. Sano Genetics (2021) (https://sanogenetics.com/condition/parkinsons-disease/)

neurodegenerative, psychiatric and stroke diseases, while in projects such as ESCAPE Bio, they focus on developing small molecules prescribed to the patient on a daily basis and that is directed to the affected area without affecting the rest of the body; continuously improving genetic studies. Countries with higher activity in this area are described in fig. 22.

Taken together, these valuable contributions reinforce the perspective of this analysis on the genetics industry, to be a sector open to collaboration with related projects, with biobanks and specialized laboratories, in addition to having specialists with a high level of commitment and dedication, in other words, a valuable and necessary human resource for the continuity of these projects and their R&D efforts.

Figure 22. Start-ups intensity in the Genetics area



The Genetics industry, although with a limited activity in the brain domain yet, is a sector that demonstrates dynamism and complexity in all facets of its clinical trials, so, despite requiring long time for its studies, it stands out in the market with specific solutions of extraordinary scientific scope, while for early or trial projects they are looking for funding quickly, attracting investors globally and opening the way to a future generation of start-ups with a defined mission and vision[23]. However, the challenges faced by early-stage projects are becoming increasingly difficult, as fewer volunteers are willing to join new trials easily, to keep their data

23 "Deals in the omics industry have increased for the first time in 9 quarters, rising by nearly 30% QoQ". CBInsights (2021)

and genetic information safe, which can be compromised, in turn exerting continuous pressure on those responsible for these studies to ensure greater privacy and to streamline research and development processes.

4. MATCHING START-UPS WITH EBRAINS TOOLS

Considering the tools already offered by the analyzed startups and their technological capacity to generate innovation, it is reasonable to believe that a significative portion of these firms can benefit of one or more services offered by the EBRAINS infrastructure, i.e. the Data and Knowledge, Atlases, Simulation, Brain-Inspired Technologies, Medical Data Analytics and Community Services.

This section tries to establish possible convergences between the technology categories on which the start-ups operate, and that Services. The identification of possible connections between the start-ups and the Services developers may give rise to opportunities for the start-ups to become users of a specific service or even collaborate with HBP researchers and/or the work packages scientific teams in the co-creation or further improvement of certain tools.

Before entering in the in-depth analysis per Service, we show below the preliminary study of such a convergence that eight different UPM´s analysts have carried out. The aggregated results can be found in table 3. In the table, red, orange, and white color cells present, respectively, a very high, high, and moderate connection potential between each category and the Services.

Table 3: Convergence between the brain technology categories and the EBRAINS Services

CATEGORY	DATA & KNOWLEDGE	ATLAS SERVICES	SIMULATION	MIP	BRAIN-INSPIRED TECH	COMMUNITY
NEUROPHARMA	VERY HIGH	VERY HIGH	VERY HIGH	VERY HIGH	HIGH	MODERATE
ARTIFICIAL INTELLIGENCE	VERY HIGH	HIGH	VERY HIGH	VERY HIGH	HIGH	HIGH
NEUROMONITORING	VERY HIGH	HIGH	VERY HIGH	VERY HIGH	MODERATE	HIGH
NEUROIMAGING	HIGH	HIGH	HIGH	HIGH	MODERATE	MODERATE
NEUROSTIMULATION	MODERATE	HIGH	HIGH	HIGH	MODERATE	MODERATE
NEW DIAGNOSIS METHODS	HIGH	HIGH	MODERATE	MODERATE	MODERATE	MODERATE
BIOMAKERS	HIGH	MODERATE	MODERATE	HIGH	MODERATE	MODERATE
VIRTUAL REALITY	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE
NEUROROBOTICS	MODERATE	MODERATE	MODERATE	MODERATE	HIGH	MODERATE
DATA ANALYSIS	HIGH	MODERATE	MODERATE	HIGH	MODERATE	MODERATE
NEUROSURGERY	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE
GENETICS THERAPY	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE	MODERATE

The analysis shows that the start-ups working in the Neuropharma sector, as well as the firms operating with Artificial intelligence solutions and Neuromonitoring tools could clearly benefit from the utilization of EBRAINS tools, especially those related to Data management, Atlas, Simulation, and the Medical Informatics platform. On the other hand, Neurosurgery, Virtual Reality and Genetics solutions would only demand EBRAINS Services moderately. Data and Knowledge Services and the Atlas, present, to some or less extent, quite interesting possibilities of connection with start-ups in practically all the technology categories studied.

The sections and diagrams below will describe now, with a higher level of detail, how useful every EBRAINS Service may be for the companies operating in each technology sub-category (see list of subcategories in chapter 3, table 1). The level of usefulness is given by the number of start-ups that, being specialized in that sub-category, could benefit from that Service. In other words, big rectangles in the diagram imply stronger relations between the EBRAINS Service and the sub-category included in that rectangle.

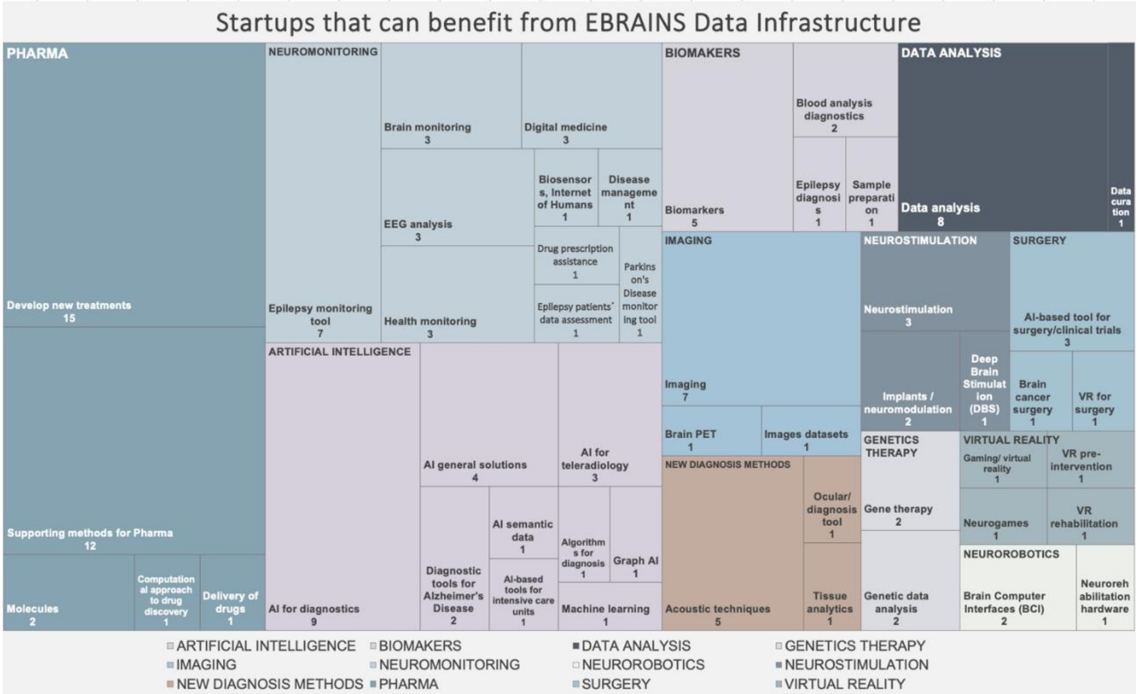
Matching with EBRAINS Data & Knowledge Services

In broad terms, within the EBRAINS Data & Knowledge services platform four main categories are offered: Knowledge Graph (KG), SANDS, OpenMINDS, along with additional support provided by a highly qualified team in Data Curation, who ensure that this data follows the FAIR principles. The KG is conceived as an open access metadata repository in which neuroscientist record information, share data and models associated with their studies, being a powerful interface that allows to establish connections (Bjaalie et al, 2021).

Given these useful properties, new knowledge is generated allowing a continuity and updating of the studies (EBRAINS, 2021), while new relationships are quickly identified. Both OpenMINDS and SANDS are applications that are part of the Data Curation service, the first as a free application that hosts and integrates the metadata schemas of the research community from GitHub expanding - among other aspects - the possibilities of connecting with external repositories; the second is its extension -also hosted on GitHub- and it standardizes certain terminologies associated with the anatomical location of the recorded data, considering for this purpose those applied in the Interactive Atlas Viewer service of EBRAINS (ibid, 2021), in order to facilitate integration with KG and, therefore, its visualization.

As shown in the figure 23, the sample of startups that can be complemented with the EBRAINS Data & Knowledge Services are specialized in the pharmaceutical field, with a strong orientation to the R&D sector in biotechnology, both in the development of medicines, and in the execution of clinical trials focused on neurodegenerative and rare diseases.

Figure 23. Start-ups matching with EBRAINS Data & Knowledge Services

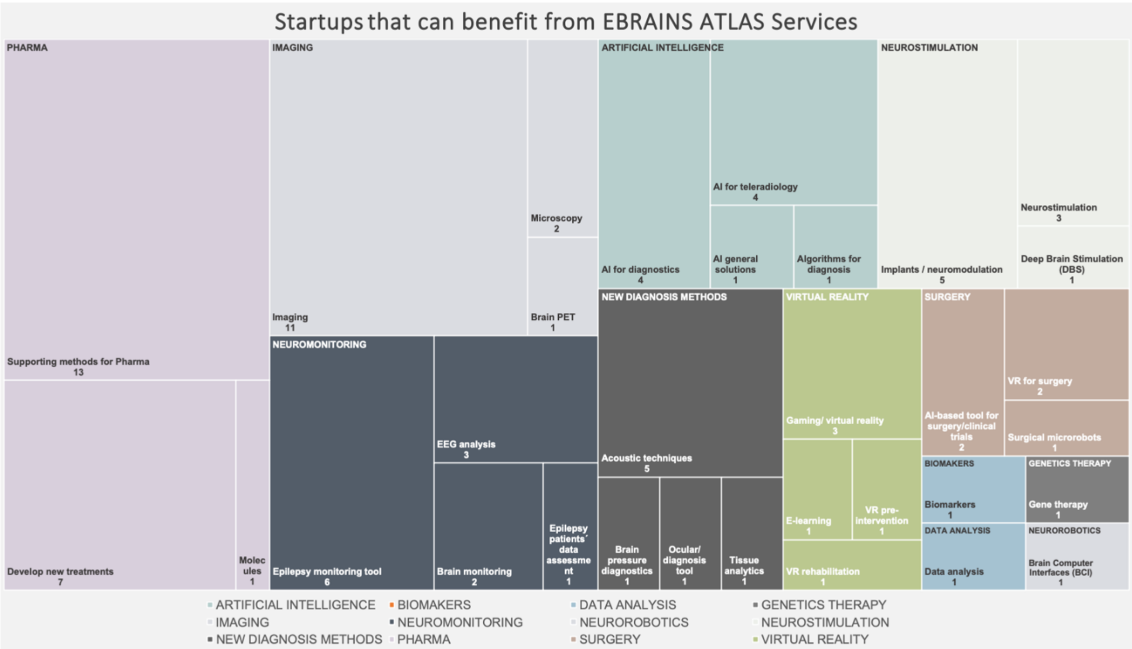


These are projects that, being in early stages, can be complemented with the repositories offered through EBRAINS, together with the advantage of executing experiments in silico from the most innovative interfaces interconnected with metadata models from other related studies. There is a group of startups that can also complement this service by developing supporting methods for Pharma through AI techniques and using in silico software for drug designs or new molecules. Interestingly, only a few of them have begun to develop solutions in quantum computing, which is considered an informatic structure that, although it is still in early stages, can analyze the molecular properties of compounds with a capacity and speed that surpasses traditional supercomputers (IBM, 2021). It is useful for EBRAINS, therefore, to be complemented soon by these new infrastructures, while in parallel these startups will manage to integrate the immense amount of data available from the neuroscientific community.

Matching with EBRAINS Atlas Services

EBRAINS has powerful 3D and 2D Atlases as the Multilevel Human Brain Atlas (Julich-Brain), the Rat Brain Atlas and the Mouse Brain Atlas, formally introduced during the HBP project and interconnected with other practical tools that allow incorporating and analysing data from neuroscientists. For example, the Multilevel Human Brain Atlas based on the Julich-Brain Atlas, was initially constructed by postmortem brain data to achieve an accurate exploration of the cytoarchitecture of the cortical and subcortical areas (Amunts et al, 2020). This results in dynamic simulation of the different levels of brain structure, on a flexible framework that facilitates the management of other interesting tools from recognised institutions and open content for the researcher, such as JUGEX, integrating genetic data from Allen Institute. Until now, in neuroscience the possibility of simulating the whole human brain in high spatial resolution remains limited (Amunts et al, 2020; Abbott, 2021), however, these are tools that have achieved a micrometric scale approximation of specific areas that play a key role in neurodegenerative diseases - such as the hippocampus, for example- or specific areas of interests, solutions that are currently available as an efficient alternative for studies requiring these delimitations.

Figure 24. Start-ups matching with EBRAINS Atlas Services



The range of possibilities offered by Julich-Brain atlas (as a fundamental axis of the EBRAINS services in Atlas) expands as it is integrated with other datasets and Atlases of international institutes that - among other aspects - enrich their anatomical and genetic structure, in a virtual interface for practical use, helpful for clinical research, pharmacological and medical device manufacturers. It is therefore a service that deploys with great precision specific areas, can be adapted to external data following the FAIR principles as part of the evaluation of therapies, and support surgical planning, as well as projects oriented to precision medicine. EBRAINS is developing an application to provide programmatic access to its users in all its Atlases during 2021 (EBRAINS, 2021), which would benefit both its research associates and the identified start-ups. It provides a platform to explore simulations immediately and scientifically based for projects, along with the ability to reflect - among other aspects - the variations of brains at the individual level in their probabilistic architecture.

Among the start-ups that could benefit from the Atlas Services (figure 24) are those that offer supporting methods for pharma with AI, through software that is developed in Python, and that can connect with other programs, evaluate datasets of molecules and new combinations, with equipment that can support their explorations to delimit or study areas of intervention. Companies that have their own simulation and prediction platforms for drugs creation can also explore alternatives with new data from other researchers, improving their AI models and accelerating scientific progress at a collaborative level.

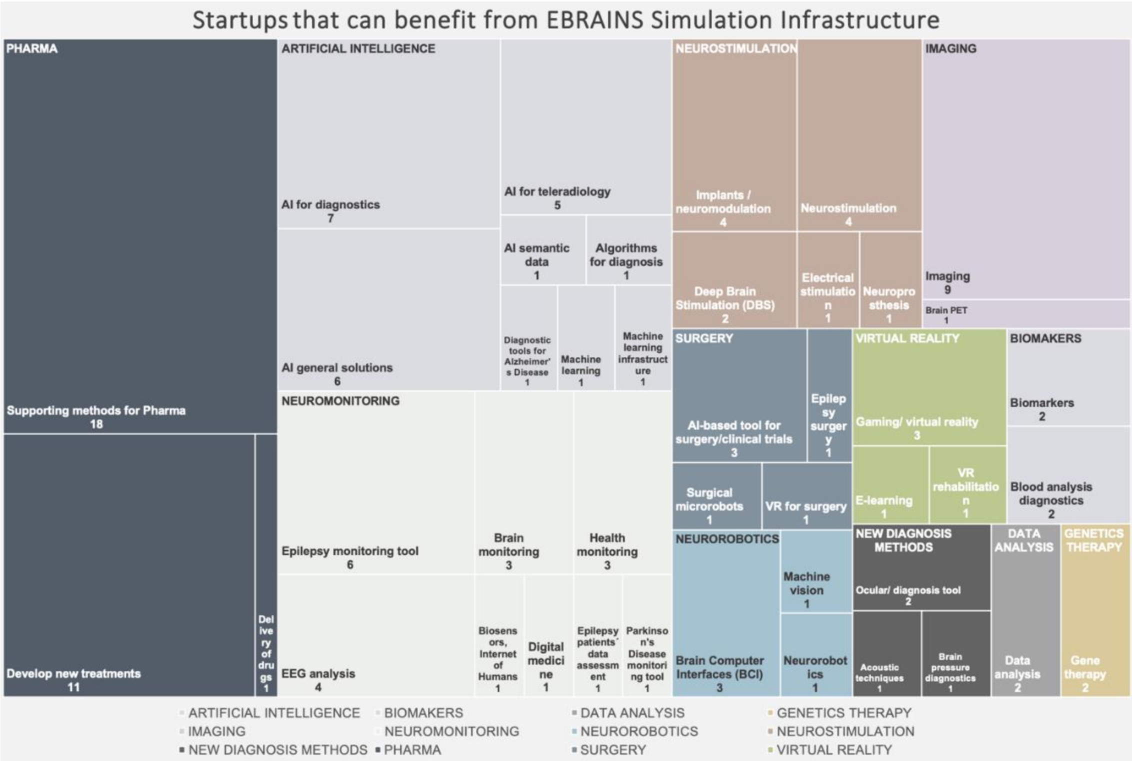
As for imaging-oriented start-ups, those that use light microscopy can further improve or accelerate current advances with the samples that are handled with this type of technology. For example, Ueda et al. (2020) explain that the powerful images achieved with this equipment would improve the construction of Atlases of the whole brain in 3D, being those the sort of applications that can be complemented with EBRAINS. In imaging, other beneficiaries of the Atlas could be those start-ups that analyze data from patients affected by neurodegenerative diseases, stroke, TBI, etc., and integrate their models with new data in this flexible and continuously evolving service, visualizing the affected areas, and also improving current surgical planning techniques based on mappings. Similarly, other beneficiary companies could be those specialized in developing more sophisticated equipment and image evaluations such as PET, MRI, MEG; they manage large amount of data, a critical matter on the evolution of Atlases. Another segment of start-ups to use the service is neuromonitoring - EEG, EMG – which offer their records in different modalities such as software, hardware, and wearables; in fact, there are already companies that apply AI for diagnosis in epilepsy, sleep disorders, movement disorders, etc.

A plethora of studies have emerged around the multiple applications that Atlases have in neuroscience. Neurosurgery, education and training, data analysis, integration of clinical and experimental data simulation, visualization of neurodegenerative diseases, among others, are fields on which companies are demonstrating an increasing interest.

Matching with EBRAINS Simulation Infrastructure

EBRAINS Services are in continuous evolution and development to offer powerful tools that allow to integrate data, simulate, and validate models. For those start-ups that evaluate models at the cellular level, the infrastructure has interactive workflows in which scientists create and simulate their data through web applications or in Python, linked to the EBRAINS platform with Jyperlab. Among other advantages, this Service facilitates the extraction of characteristics of electrophysiological records to build detailed models of neuronal connectivity, analysis and visualization of data in silico in variable brain sizes (EBRAINS, 2021).

Figure 25. Start-ups matching with the EBRAINS Simulation Infrastructure



Start-ups specialized in pharma and supporting methods for pharma (see figure 25), focused in molecular simulation for drug design or in silico modelling of proteins, could be complemented with Arbor to study both the morphology of individual cells and groups of cells, 3D modeling of brain areas or neuronal groups and their synapses, according to the areas to be intervened. In this sense, applications like NeuroTessMesh, NeuroScheme, ViSimpl, and NEST are just few examples of the most modern and varied tools that these start-ups can explore, adapting them to their own experiments. Those companies that develop solutions based on Neuromonitoring with EEG records, as well as AI analysis, can find in Elephant a useful open-source application to evaluate simulations based on electrophysiology, with the possibility of visualizing graphs for analysis and practical tutorials of easy access.

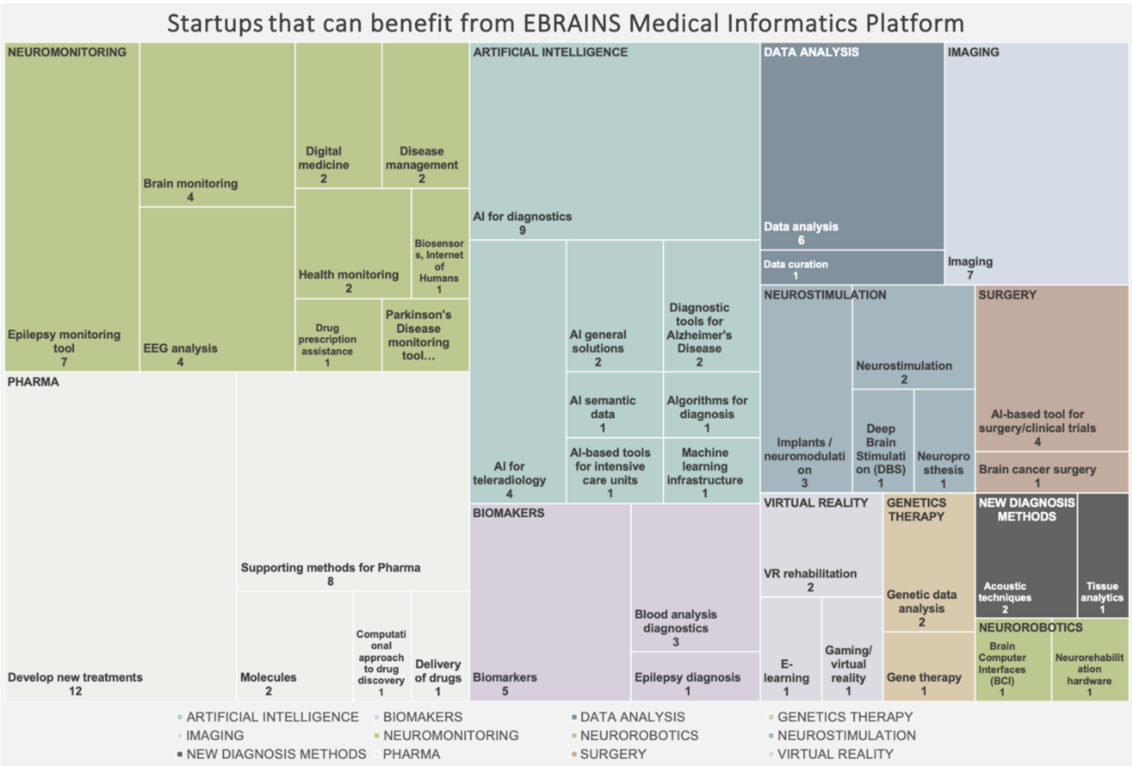
Start-ups that continuously develop AI solutions, which require optimizing and improving the accuracy of their models and associated medical devices, can evaluate neurological conditions such as TBI, Stroke, epilepsy, for example, through The Virtual Brain (TVB), Those start-ups that seek to transfer their studies in VR or AR, have an outstanding frame of reference in this platform.

Projects based on medical devices for surgical intervention can ALSO use these services as a reference in the planning of the areas to be intervened, in addition to comparing them with their current intervention strategies.

Matching with EBRAINS Medical Informatics Platform

One of the services that stands out within EBRAINS is the analysis of medical data worldwide with the Medical Informatics Platform (MIP), an open-source technology that rests on a federated structure of privacy-preserving at four main levels, allowing data to be shared without being breached. At the first level, the front-end level or portal, the data of the medical service and the associated centers are visualized and explored, incorporating in their evaluation recommended and personalized algorithms for the clinical researcher, and providing statistical graphs. A second level or MIP Federated, allows the integration of anonymized data (HER, imaging) through specialized tools, also as support for users in the transfer process, defined in a scheme known as Common Data Elements (CDEs), keys to the identification of the brain structure of patients, diagnoses, clinical results, etc. (see Demiraj et al, 2019). The third level comprises the local version deployed in each hospital to perform its own analyses, while the last level or MIP Data Factory integrates the data to be analyzed (ibíd, 2019).

Figure 26. Start-ups matching with EBRAINS Medical Informatics Platform



Being the MIP a useful and easy-to-use structure for the sharing and evaluation of medical data on an international scale, it seems to be an opportunity for the health service to use the MIP to provide greater precision in diagnoses, reducing errors and achieving an efficient planning of therapies. It is, therefore, relevant the number of start-ups, clinical teams and new projects that can benefit from the platform as shown in the figure 26, most of them oriented in pharma, neuromonitoring, AI, and biomarkers. Clearly, these are start-ups that handle large amount of data that can be integrated into the platform and in turn benefit from virtual experiments, compare studies, and request custom algorithms in specific datasets. For pharma start-ups, this would help optimize the processes prior to the start of their clinical trials, in addition to considering data from dozens of centers in completed trials, saving significant costs, and accelerating new studies.

For start-ups specialized in neuromonitoring, the advantages of incorporating a free-to-use platform into their routines are enormous in terms of AI, with a focus in identifying signals in specific disease conditions - epilepsy, Alzheimer, Parkinson and rare diseases. In addition, those companies focused on biomarkers could also explore possibilities in the MIP, by having in the platform data from brain scans, MRI, or her, including medications, and laboratory test results.

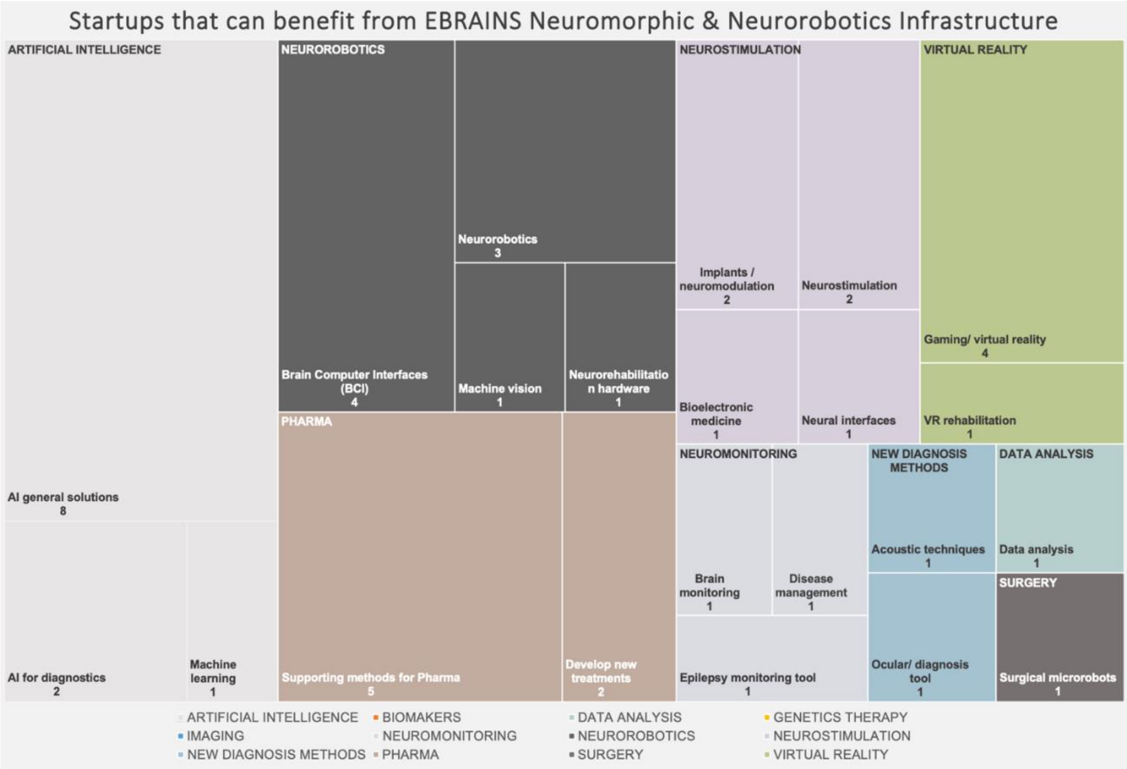
Matching with EBRAINS Neuromorphic & Neurorobotics Infrastructure

Other applications that are currently booming worldwide are AI in Robotics, a scientific area available in this infrastructure through tools like the Neuromorphic Computing or Neurorobotics Platforms. They provide less energy consumption and extraordinary capacity for simulation and emulation of neural networks in real time. In simplified terms, start-ups specialized in this field, or those that intent to simulate their models in robots, can be supported with the Neuromorphic Computing system, composed of BrainScaleS (based in Heidelberg) and SpiNNaker (Manchester), with the advantage of reflecting the synaptic plasticity (EBRAINS, 2021).

Start-ups working on AI general solutions and AI for diagnostics (see figure 27) can use neuromorphic processors that seek to reduce their energy consumption. They can also complement their results with these simulations. Other applications include projects developed with neuromorphic chips for processing voice signals or neuromorphic hardware, showing most of them still quite limited technical capabilities.

Some startups have managed to develop robotic structures for rehabilitation in patients affected by neurological diseases, with complementary interfaces that allow communication with doctors to optimize therapeutic programs and manage patient data. They could, therefore, evaluate the possibility of experimenting with these tools, through the responses of users when using medical devices, to know in depth the dynamics of plasticity or regions affected for learning and memory, through simulations. Some successful and innovative projects in the educational field, supported by EBRAINS, have created robot assistants or companions, such as the MiRo project or social robot (see Consequential Robotics, 2021).

Figure 27. Start-ups matching with EBRAINS Neuromorphic & Neurorobotics Infrastructure

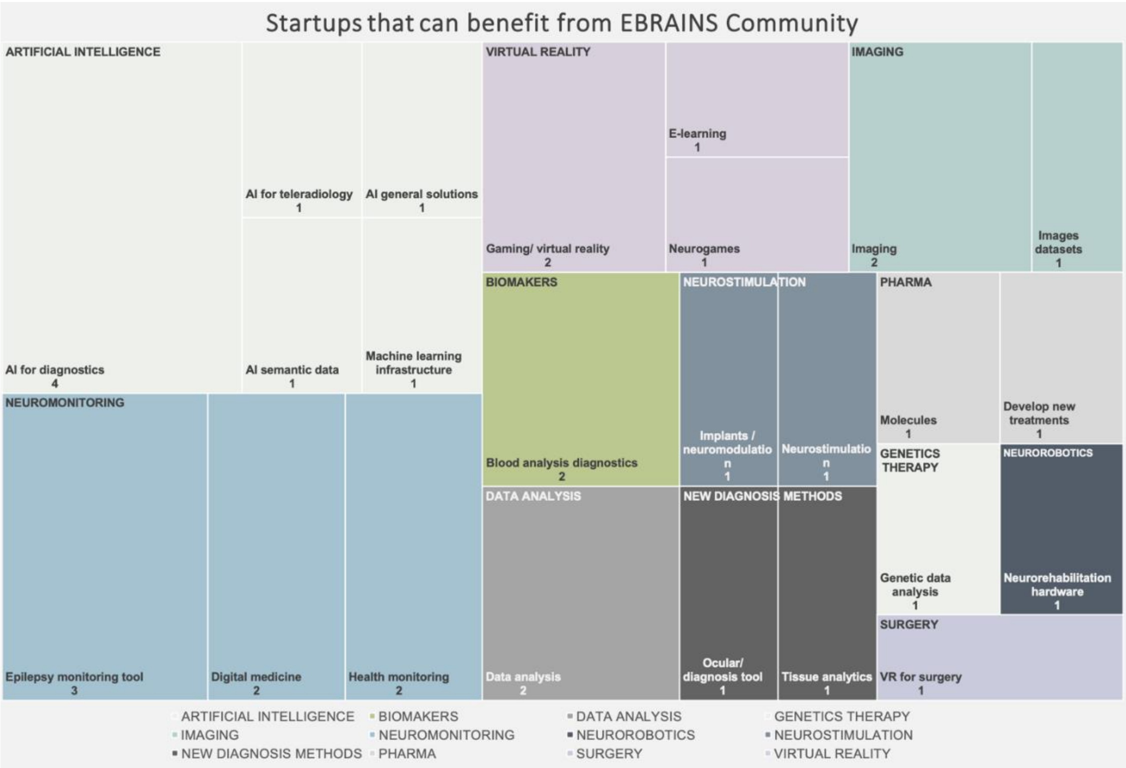


Start-ups that excel in Brain Computer Interfaces (BCI) and develop brain implants to combat neurodegenerative diseases and as alternatives for patients who do not respond adequately to other interventions such as DBS, can also benefit from the EBRAINS Neuromorphic & Neurorobotics Infrastructure. Projects that track eye movements and brain signals, with a strong inclination to AI and neuromorphic computing, can deploy their models with these EBRAINS tools. EBRAINS has guides, manuals, videos, and online collaboration support for those interested (see HBP_SP9_Specification, 2020), available on its Collaboratory platform.

Matching with EBRAINS Community Services

The Collaboratory service offers an online workspace for the exchange of data and editing of documents between scientific teams in a secure way (Schirner et al, 2021). The researcher controls the amount of information to share with his groups or specific users, accessing an organised space and to connect with other researchers, facilitating networking, online collaboration, necessary activities for new entrepreneurs and ongoing projects. The possibility of learning about the work of multidisciplinary teams, on a dynamic virtual space, facilitates the exchange of ideas, the access to multimedia content, guides, tutorials, and the publication of activities of interest to other groups. The users of the EBRAINS Collaboratory can store data from their own research, it is free and does not require installation.

Figure 28. Start-ups matching with EBRAINS Community Services



In general, the Collaboratory is a service of interest for users who wish to take advantage of the infrastructure, have a reliable workspace to start exploring data from other publications, share doubts and suggestions. Subgroups have been created for Brain Atlases, Brain-Inspired Adaptative Cognitive Architectures, Consciousness and Cognition, Data Driven Simulations, Data Sharing and Knowledge, High Performance Computing (HPC) and Cloud Computing, Neuromorphic Computing (NMC), Neurorobotics, Responsible Research and Innovation in Neuroscience, Simulation Engines, and the Virtual Brain (TVB).

In this sense, start-ups specialized in AI applied to diagnoses, teleradiology, or AI semantic data could benefit from these subgroup spaces (see figure 28); they can share models, consult with researchers, and find useful tools to improve their value proposition. Start-ups in the Neuromonitoring area, especially those that have developed applications to record brain electrical signals in epilepsy, digital medicine and health monitoring may also benefit. Other users could be the start-ups specialised in virtual reality, which have a space and relevant material on the TVB. Companies operating in data analysis and simulation can find interesting information on brain models and tissues, compare studies, and discuss with other scientists interested in the area. The EBRAINS Community Services represent, in sum, an important opportunity for start-ups to connect with international researchers, generate practical spaces for discussion, and boost collaborative learning.

5. CONCLUSION

Our mapping of start-ups has helped us to understand in what direction, geographically and thematically, brain innovation is evolving in Europe. The study of the companies´ publicly available information, together with the intensive searching of signals on their business performance, not only have allowed us to corroborate some general ideas we had on the characteristics of this type of firms, but also served to present some insights on aspects of brain-technologies that could eventually make the activity of these start-ups different.

A **first** conclusion that have probably already captured the reader´s attention is the very broad and varied range of technology areas currently addressed by the companies in the sector. Our bottom-up identification of categories (12) and sub-categories (62) contributed to see the brain-technology innovation activity as a domain with multiple angles, a field of work that indeed require multidisciplinary attention and the exploration of problems, very frequently, from radically different perspectives. Regardless the granularity and the specificness of some identified technology areas, the products and services developed have, in general, a great significance and impact potential, not least because both the fighting against brain diseases -in any of their manifestations - and the tremendous ambition to map, learn and devise applications based on the functioning of the human brain are huge challenges with extraordinary influence on Society. The relevance of these challenges seems to stimulate the creation of awards and institutional endorsements that distinguish valuable entrepreneurial efforts made by some of these companies, and the recognition of their most important innovations.

As a **second** conclusion, it seems imperative to foster the interaction between European start-ups, thus promoting knowledge circulation and technological synergies, and to design joint initiatives, like the formation of consortia to apply for funds together with larger companies. The creation of start-ups associations would in addition bring the voice of the start-ups more efficiently and stronger to the policy spheres. Such an interaction would contribute to materialise more quickly a European Brain Initiative and consolidate a brain innovation ecosystem. In fact, joining forces would make easier the practical approaching of the start-ups to other actors of the innovation landscape. Common practices identified, like data sharing or the utilisation of federated or distributed tools, are evidence of the predisposition found in the analysed companies to collaborate.

A **third** point to highlight is related to the geographical analysis. Although we have identified some places where brain innovation is happening more intensively, we cannot conclude that there is a very marked specialisation in the European regions, except for France, which shows a strong leadership in Neuropharma. The market scope has, however, a global in most of the cases. It is also interesting to observe that the most notable advances are made by countries that also present adequate conditions for innovation according to the EIS indicators.

A **fourth** message refers to the convergence of the start-ups with EBRAINS. In fact, our matching analysis has indicated that multiple opportunities exist to connect, commercially or in terms of collaboration, the companies to the services offered by the infrastructure. Companies working in the Neuropharma sector, and firms operating with Artificial intelligence solutions and Neuromonitoring tools are the ones that could benefit most of the Services offered. In this regard, the authors would like to strongly encourage HBP and EBRAINS teams to review the list of start-ups included in the annexe, so that to select the most interesting ones with respect to the utilisation of Services and establish channels to connect and invite them to check the utility of your tools.

Future versions of this report will be regularly made by the UPM to inform on other activities undertaken by the analysed companies, identify new ones, and elaborate on specific aspects like the dynamics of investing stakeholders, the influence of companies´ size, or their contribution to job creation.

To provide this report with a very practical and pragmatic perspective we decided to illustrate theoretical reflections and the discussions with real examples and practices of companies actively working in the brain area. Geographical restrictions to the European context, and limitations with respect to the age of the companies – 10 years maximum – have been self-imposed to make the sample size manageable. The good quality of data obtained, the representativeness of the start-ups analysed, and the meticulous methodology utilised have contributed to make our results and conclusions, in our opinion, highly generalisable.

ANNEXE: START-UPS

FAMILY	CATEGORIES	COMPANY	COUNTRY	FOCUS
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	CAUSALY	UK	Answer complex questions from Biomedicine and Healthcare within seconds
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	CELLARI	UK	Store clinical and research data
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	GRAYSCALE	UK	Optimization-driven AI, meant to mimic a human's neural network
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	MINDTRACE	UK	Deploying a novel, disruptive, brain-inspired AI solutions to enterprise clients
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	NEUROBOTX	UK	Capture your laboratory data and protocols with AI in healthcare services
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	AICTX / SYNSENSE	SWITZERLAND	AiCTX is developing "full-stack" custom neuromorphic processors for a variety of artificial-intelligence (AI) edge-computing applications that require ultra-low-power and ultra-low-latency features, including autonomous robots, always-on co-processors for mobile and embedded devices, wearable health-care systems, security, IoT applications, and computing at the network edge.
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	ALPINE INTUITION	SWITZERLAND	Crafting innovative tools and solutions based on machine learning, deep learning and AI
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	DENAPSIS	SWEDEN	Interpret and predict genomic and genetic variants, epigenetic modifications such as DNA methylation or protein binding, RNA expression, protein, biomarkers etc.
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	AMBERSCRIPT	NETHERLANDS	Get text from the recorded voice or video
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	FRANKIE HEALTH	IRELAND	B2B Mental Health platform. Providing services to companies that lack mental health programs and specialists for their employees
ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	CARTESIAM	FRANCE	Empower companies to quickly, easily and cost-effectively integrate AI into their projects.

ARTIFICIAL INTELLIGENCE	AI GENERAL SOLUTIONS	PROPHESEE	FRANCE	PROPHESEE creates both neuromorphic sensors and bio-inspired algorithms that function like the eye and brain. This holistic approach is a fundamental shift in computer vision – the departure from frame-based sensors, to event-based vision systems. Each pixel only reports when it senses movement. Whereas in a frame-based sensor all pixels record at the same time, in an event-based sensor each pixel is perfectly independent.
ARTIFICIAL INTELLIGENCE	AI SEMANTIC DATA	SEMANTIC INTELLIGENCE	LATVIA	Search, analyse and extract complex knowledge on chemical-biological interactions
ARTIFICIAL INTELLIGENCE	AI SPECIFIC TOOLS FOR ALZHEIMER DIAGNOSIS	OXFORD BRAIN DIAGNOSTICS LTD	UK	Dementia, Alzheimer's disease diagnosis at the earliest opportunity
ARTIFICIAL INTELLIGENCE	AI SPECIFIC TOOLS FOR ALZHEIMER DIAGNOSIS	CONECTIVA	SPAIN	Diagnostics of brain diseases
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	CLEARSKY MEDICAL DIAGNOSTICS	UK	Automated assessment of Parkinson's and other neurodegenerative conditions, with a number of clinical studies underway.
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	NORDIC MEDTECH AB	SWEDEN	Cutting-edge technology solutions for healthcare in the form of Artificial Intelligence aimed at neurological diseases.
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	METHINKS	SPAIN	Provide universal and timely diagnosis
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	SPOTLAB	SPAIN	New generation of telemedicine solutions to reduce the time, costs, distances and carbon footprint of medical diagnosis.
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	BRAINSCAN	POLAND	Decrease the errors of CT evaluations
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	ADA HEALTH	GERMANY	Give users a trustworthy health assessment within a digital network. Help the client's users choose the right clinical or virtual care services with customizable care navigation. Securely transform users' assessment reports into a desired medical professionals' IT system. Manage care demand and supply during the COVID-19 pandemic
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	FUSE-AI	GERMANY	Improve radiological examinations
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	INVEOX	GERMANY	Risk of operational irregularities and potential misdiagnoses are significantly reduced and patient safety – especially in cancer diagnostics
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	VICRON	GERMANY	Optimize the utilization of medical resources

ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	INCEPTO MEDICAL	FRANCE	Help medical workers to analyse vast amount of data with greater accuracy
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	PIXYL	FRANCE	Using deep-learning-based solutions in order to track disease activity and progression in neurodegenerative diseases like multiple sclerosis or Alzheimer disease to improve patient care.
ARTIFICIAL INTELLIGENCE	AI-BASED DIAGNOSIS	SANCARE HEALTH AND DATA	FRANCE	The company's platform incorporates the use of machine learning to recognize the pathologies described in a patient file and to deduce the performed hospital acts, providing doctors and medical professionals with relief in terms of the tedious administrative work and allows hospitals to charge more accurately their activity to the health Insurance.
ARTIFICIAL INTELLIGENCE	AI-BASED TELERADIOLOGY	NICO.LAB	NETHERLANDS	AI supported CT Scan analysis to detect anomalies with stroke incidents
ARTIFICIAL INTELLIGENCE	AI-BASED TELERADIOLOGY	QUANTIB	NETHERLANDS	Automated segmentation of brain structures and white matter hyperintensities.
ARTIFICIAL INTELLIGENCE	AI-BASED TELERADIOLOGY	GRAID	HUNGARY	Create reports in a highly faster way
ARTIFICIAL INTELLIGENCE	AI-BASED TELERADIOLOGY	DEEPC	GERMANY	Turn medical data into insights for diagnostics
ARTIFICIAL INTELLIGENCE	AI-BASED TELERADIOLOGY	MILVUE	FRANCE	Diagnostic tool aimed to support emergency rooms radiographs
ARTIFICIAL INTELLIGENCE	AI-BASED TELERADIOLOGY	CEREBRIU	DENMARK	solutions to automate radiology workflows, improve brain MRI efficiency, improve patient prioritisation, and reduce scan time, re-examinations, and non-acute admissions.
ARTIFICIAL INTELLIGENCE	AI-BASED TOOLS FOR INTENSIVE CARE UNITS	CLINOMIC	GERMANY	Smart bedside assistant for the Intensive Care Unit
ARTIFICIAL INTELLIGENCE	ALGORITHMS FOR DIAGNOSIS	BRAINTALE	FRANCE	Develops and distributes accessible and effective diagnosis and prognosis tools for brain injured patients
ARTIFICIAL INTELLIGENCE	GRAPH AI	LYNXKITE	HUNGARY	LynxKite is to graph databases what RapidMiner and IBM SPSS Modeler are to SQL databases. But it is not necessary to have a graph database to use LynxKite as it manages its own internal graph data model.
ARTIFICIAL INTELLIGENCE	MACHINE LEARNING INFRASTRUCTURE	GETNEURO	UK	Accelerate ML development for engineers and data scientists without servers and payments for computing time
ARTIFICIAL INTELLIGENCE	MACHINE LEARNING SOLUTIONS	BIAS VARIANCE LABS	SLOVENIA	Facilitates data-to-discovery process by focusing on cutting-edge approaches from artificial intelligence and data science.

BIOMARKERS	BLOOD ANALYSIS DIAGNOSIS	ILOF	PORTUGAL	The company uses AI and photonics to build a cloud-based library of diseases biomarkers and biological profiles, and provide screening and stratification tools in an affordable, fast, portable way.
BIOMARKERS	BLOOD ANALYSIS DIAGNOSIS	AGENT	FRANCE	Alzheimer's detection long before the dementia symptoms
BIOMARKERS	BLOOD ANALYSIS DIAGNOSIS	NIGHTINGALE HEALTH OYJ	FINLAND	Blood analysis technology utilises NMR (nuclear magnetic resonance) and proprietary software to provide comprehensive health data that links a person's lifestyle to their disease risk
BIOMARKERS	EPILEPSY DIAGNOSIS	NEURONOSTICS LTD	UK	Faster and more accurate diagnosis and prognosis of epilepsy
BIOMARKERS	GENERAL BIOMARKERS	POCKIT DIAGNOSTICS	UK	Stroke detection
BIOMARKERS	GENERAL BIOMARKERS	ND BIOSCIENCES	SWITZERLAND	Powerful proprietary technologies and innovative tools that enable for the first time reproducing, at both the biochemical and structural levels, the proteoforms and pathological species found in the brain and biological fluids of patients suffering from neurodegenerative diseases
BIOMARKERS	GENERAL BIOMARKERS	TIME IS BRAIN	SPAIN	Improving diagnostics, treatment and prognosis of patients suffering acute ischemic stroke (AIS)
BIOMARKERS	GENERAL BIOMARKERS	HEAD DIAGNOSTICS	IRELAND	Handheld medical device for the rapid assessment and evaluation of brain impairment and brain disease. The device is unique in targeting a little-known physiological window into brain activity. Planned to be used in a range of conditions, including TBI, Parkinson's Disease, stroke, and other degenerative brain diseases.
BIOMARKERS	GENERAL BIOMARKERS	MEDICORTEX	FINLAND	Improving the diagnosis, treatment and prevention of acute neurodegenerative conditions
BIOMARKERS	GENERAL BIOMARKERS	PROTEOFORMIX	BELGIUM	Innovative biomarkers which will allow rapid and accurate diagnosis of multiple disorders simultaneously in a single patient's small-volume sample.
BIOMARKERS	SAMPLE PREPARATION	SCIPIO BIOSCIENCE	FRANCE	A powerful benchtop kit to extract mRNA from single cells anytime, anywhere.
DATA ANALYSIS	DATA ANALYSIS	BRAIN WAVE BANK	UK	Gathering data for central nervous system disorders
DATA ANALYSIS	DATA ANALYSIS	DEEPPSY	SWITZERLAND	Treatment personalization
DATA ANALYSIS	DATA ANALYSIS	IOMED	SPAIN	Improve health data quality and management for medical research

DATA ANALYSIS	DATA ANALYSIS	CLIMEDO HEALTH	GERMANY	A cloud-based platform for cutting-edge clinical validation and post-market surveillance of medical devices and pharmaceutical products
DATA ANALYSIS	DATA ANALYSIS	ARCA SCIENCE	FRANCE	AI tool and a next-gen search engine able to tap into and leverage massive biomedical data.
DATA ANALYSIS	DATA ANALYSIS	CYBERNANO	FRANCE	Contract Research Organization in Biostatistics for Risk Assessment and Quality Optimization
DATA ANALYSIS	DATA ANALYSIS	ASPECT ANALITICS	BELGIUM	Manage large amounts of rich but complex data (mainly from Mass spectrometry imaging (MSI) experiments)
DATA ANALYSIS	DATA ANALYSIS	HELPILEPSY (NEUROVENTIS)	BELGIUM	Mobile application that users can enter their log, and review analysis. And doctor can analyse data
DATA ANALYSIS	DATA CURATION	LONGENESIS	LATVIA	Developing legitimate ways to promote collaboration between biomedical institutions, patient organizations and research partners by identifying biomedical data from metadata files, by onboarding population cohorts and by engaging new patients in the research. This is achieved through the implementation of a universal toolkit, comprised of three interrelated modules.
GENETICS THERAPY	GENE THERAPY	AVRION TX	SWITZERLAND	Genetically-linked neurodegenerative diseases
GENETICS THERAPY	GENE THERAPY	POLYQURE	PORTUGAL	SCA3 disease (Ataxia), poliQ diseases
GENETICS THERAPY	GENETIC DATA ANALYSIS	SANO GENETICS	UK	Upload and control of DNA data
GENETICS THERAPY	GENETIC DATA ANALYSIS	CARTANA	SWEDEN	Mapping of gene expression in tissue via revolutionary In Situ Sequencing (ISS) technology.
IMAGING	BRAIN PET	POSITRIGO	SWITZERLAND	Improve diagnostic on dementia, AD
IMAGING	DATASETS - IMAGES	AIGORA	GERMANY	High quality medical image datasets accessible to AI researchers and developers
IMAGING	MICROSCOPY	DOITPLENOPTIC	SPAIN	Transform any microscope into a 3D & 4D digital microscope. Just like compound insect eyes work. The microlenses array, capture multi-perspective images that unveil the hidden volumetric information in real-time

IMAGING	MICROSCOPY	CONFOCAL.NL	NETHERLANDS	Improve the microscopic imaging experience of all researchers. Upgrade solutions to turn any microscope into a 3D confocal microscope with extreme sensitivity and super resolution. Confocal.nl microscope systems are available for the visible, and also near-infrared, imaging spectrum.
IMAGING	NEUROIMAGING	CORTIRIO	UK	Traumatic brain injury
IMAGING	NEUROIMAGING	3BRAIN	SWITZERLAND	3Brain strives to provide researchers with breakthrough technology to improve the understanding of organs and their related illnesses
IMAGING	NEUROIMAGING	MEDIMSIGHT	SPAIN	Allows clinicians to acquire software solutions in a single platform
IMAGING	NEUROIMAGING	QMENTA	SPAIN	Digital Healthcare, Neuroimaging, Mobile Health, IT, Clinical trials, Brain, Data analysis, Data management, Imaging biomarkers, Artificial Intelligence
IMAGING	NEUROIMAGING	QUBIOTECH HEALTH INTELLIGENCE	SPAIN	Allows clinicians to detect abnormalities in PET, SPECT, MRI
IMAGING	NEUROIMAGING	B2QUANT	PORTUGAL	Experience in multiple sclerosis, dementia and cerebral small vessel disease
IMAGING	NEUROIMAGING	TI-COM, LLC	POLAND	Platform for the delivery of therapeutic agents based on biomaterials and image-guided neurointerventions to achieve unprecedented precision and reproducibility
IMAGING	NEUROIMAGING	ADVANTIS MEDICAL	NETHERLANDS	Make medical Imaging more accessible, user-friendly and data-driven by merging it with cloud technology.
IMAGING	NEUROIMAGING	PIONIRS	ITALY	Faster and more accurate disease diagnosis. Real-time, non-invasive brain measurements. Effective muscle oxygenation monitoring. Brain-machine interface (BMI). Absolute tissue optical properties retrieval.
IMAGING	NEUROIMAGING	ELMINDA	ISRAEL	Revolutionary new way to understand how the brain’s neural networks are activated and inform about brain function.
IMAGING	NEUROIMAGING	MEDIAIRE	GERMANY	Early detection and differentiation of Dementia, as well as assessment of lesion dynamics in Multiple Sclerosis
IMAGING	NEUROIMAGING	MAG4HEALTH	FRANCE	The first non-invasive bio magnetic imagery tool that provides high spatial and temporal resolutions
IMAGING	NEUROIMAGING	SEENEL IMAGING	FRANCE	Seenel Imaging is dedicated to functional Neuroimaging technology

IMAGING	NEUROIMAGING	THERAPANACEA	FRANCE	The radiation oncology workflow involves a series of manual, tedious tasks adding even more to an already significant and frequently overwhelming clinician workload
IMAGING	NEUROIMAGING	ICONEUS	FRANCE	Pre-clinical functional ultrasound (fUS) imaging of brain activity and vasculature.
IMAGING	NEUROIMAGING	ICOMETRIX	BELGIUM	Multiple sclerosis, brain trauma, epilepsy, stroke, dementia, and Alzheimer's disease
NEUROMONITORING	BIOSENSORS & INTERNET OF HUMANS	IDUN	SWITZERLAND	Understand human emotion and cognition through wearables
NEUROMONITORING	BRAIN MONITORING	LUCIOLE MEDICAL AG	SWITZERLAND	Effective and reliable solution for brain oxygen measurement
NEUROMONITORING	BRAIN MONITORING	SCIGNALS	SPAIN	Recording and processing biomedical signals in the health field
NEUROMONITORING	BRAIN MONITORING	BIOSERENITY	FRANCE	Precision in diagnosis related to brain diseases, sleep disorders and cardiology
NEUROMONITORING	BRAIN MONITORING	BRAINDEX	FRANCE	Brain functions monitoring device for clinicians during surgery
NEUROMONITORING	BRAIN MONITORING	NEUROVENTIS	BELGIUM	Neuroventis platform, a specialized tool that features a user-friendly dashboard for healthcare professionals
NEUROMONITORING	BRAIN MONITORING	NORGANOID	AUSTRIA	Modelling of individual illness and screening of drugs more accurately with the capacity of reducing animal testing.
NEUROMONITORING	DIGITAL MEDICINE	VIDA APP	SPAIN	Prevent Alzheimer
NEUROMONITORING	DIGITAL MEDICINE	NORDIC BRAIN TECH AS	NORWAY	Home-based migraine treatment
NEUROMONITORING	DIGITAL MEDICINE	REDUCEPT	NETHERLANDS	Combination of scientific insights on pain education, psychology and digital therapy, to develop an unique method to manage and treat chronic pain
NEUROMONITORING	DISEASE MANAGEMENT	VCREATE LTD | FOUNDER	UK	NHS Trusted Secure Video Service for Clinical Care. The cloud-based service allows registered patients or their carers to securely share smartphone-recorded videos and associated metadata with their clinical team to asynchronously digitise diagnostic and therapeutic decision-making processes.
NEUROMONITORING	DISEASE MANAGEMENT	COGNUSE	ESTONIA	Design highly integrative digital tools to help guide clients through the recovery process
NEUROMONITORING	DRUG PRESCRIPTION TOOLS	SYNAPSE MEDICINE	FRANCE	Provide easy access to reliable, up-to-date, and fully independent medical information to everyone who needs it.
NEUROMONITORING	EEG ANALYSIS	NEWMANBRAIN	SPAIN	Correlate the activity of diverse areas of the brain with mental functions

NEUROMONITORING	EEG ANALYSIS	MBRAINTRAIN	SERBIA	Next-generation EEG device for any EEG experiment set-up you can think of
NEUROMONITORING	EEG ANALYSIS	NEUROPLAY	POLAND	NeuroPlay is a response to the growing need to improve the cognitive functioning of older people, and thus the quality of their life and everyday functioning. Regular cognitive training using the EEG-biofeedback method is an effective tool in the process of preserving and improving cognitive abilities in the aging process.
NEUROMONITORING	EEG ANALYSIS	NEUROCONNECT	ITALY	Transfer the long members experience and expertise in the basic and clinical research in providing highly qualified services
NEUROMONITORING	EEG ANALYSIS	CERENION OY	FINLAND	Cerenion C-Trend® -powered EEG devices provide a new level of ease and confidence in monitoring the neurophysiological status of patients
NEUROMONITORING	EPILEPSY MONITORING TOOLS	EMOSYS	NETHERLANDS	Focus on addressing and ending the burden of epileptic seizures
NEUROMONITORING	EPILEPSY MONITORING TOOLS	NIGHTWATCH	NETHERLANDS	Detect possible severe epileptic seizures at night
NEUROMONITORING	EPILEPSY MONITORING TOOLS	BRAINCARE OY	FINLAND	Simplify seizure monitoring
NEUROMONITORING	EPILEPSY MONITORING TOOLS	BYTEFLIES	BELGIUM	Help people with seizures, improve diagnostics and therapy
NEUROMONITORING	EPILEPSY MONITORING TOOLS	EPIHUNTER	BELGIUM	APP for epilepsy. Wearable absence seizure tracker
NEUROMONITORING	EPILEPSY MONITORING TOOLS	NILE	BELGIUM	Epilepsy
NEUROMONITORING	EPILEPTIC PATIENTS´ DATA ASSESSMENT	NEURO EVENT LABS	FINLAND	Help people with seizures, improve diagnostics and therapy of Epilepsy
NEUROMONITORING	HEALTH MONITORING	SIDEKICKHEALTH	SWEDEN	Combines behavioural economics, gamification and artificial intelligence for an engaging experience that removes barriers to health behaviour change and expands the possibilities of well-being.
NEUROMONITORING	HEALTH MONITORING	EB2 - EVIDENCE BASED BEHAVIOR	SPAIN	Mental health, emotional well-being and chronic illnesses
NEUROMONITORING	HEALTH MONITORING	ILURIA LTD	ISRAEL	Attention deficit hyperactivity disorder

NEUROMONITORING	PARKINSON MONITORING TOOLS	PARAGIT	DENMARK	Helping people suffering from motor-related disorders
NEUROMONITORING	PARKINSON MONITORING TOOLS	WALK WITH PATH	DENMARK	Mobility solutions that help activate the motor cortex in the brain. The device helps brain initiate movement and a laser line helps resume walking in Parkinson´s patients
NEUROROBOTICS	BRAIN COMPUTER INTERFACES	BRAINALIVE	UK	BrainAlive uses computer vision and neuroscience to provide a revolutionary feedback on user engagement
NEUROROBOTICS	BRAIN COMPUTER INTERFACES	MINDAFFECT	NETHERLANDS	Open-source code solution to make your own Brain Computer Interface (BCI) application that is reliable, fast and requires no training
NEUROROBOTICS	BRAIN COMPUTER INTERFACES	BRAINGRADE GMBH	GERMANY	Alzheimer's disease, dementia
NEUROROBOTICS	BRAIN COMPUTER INTERFACES	CEREGATE	GERMANY	Provide patients with neurological disorders or sensory deficits with new opportunities to adapt and improve their condition
NEUROROBOTICS	MACHINE VISION	BIORETICS	ITALY	End-to-end systems from idea to ready-to-market devices in cooperation with our business partner.
NEUROROBOTICS	NEUROREHABILITATION HARDWARE	BRAIN STIMULATION AB	SWEDEN	Rehabilitating need for cognitive and upper limb impairments after stroke and acquired brain injuries, by exploiting brain plasticity results from research within a new concept of rehabilitation and diagnosis of cognitive impairments.
NEUROROBOTICS	NEUROREHABILITATION HARDWARE	YAKNA	CZECH REPUBLIC	Refine the diagnosis of subsequent rehabilitation
NEUROROBOTICS	NEUROROBOTICS	CONSEQUENTIAL ROBOTICS	UK	CR delivers the best of British & international design and engineering to the development of next generation consumer and commercial robots. IP portfolio includes innovations developed with researchers at the University of Sheffield in the areas of mechatronic design and "brain-based" biomimetic control.
NEUROROBOTICS	NEUROROBOTICS	AUTONOMYO	SWITZERLAND	Individual fitting, training program and customised walking assistance
NEUROROBOTICS	NEUROROBOTICS	BRAINTRONIX	ROMANIA	Robots for navigate indoor and outdoor in order to facilitate client needs
NEUROSTIMULATION	BIOELECTRONIC MEDICINE	GALVANI BIOELECTRONICS	UK	Therapies to treat disease through implant-based direct modulation of specific neural signals to organs in chronic disease.

NEUROSTIMULATION	DEEP BRAIN STIMULATION	NI20	UK	Continuing the work started by MIT's Mind Machine Project – developing a revolutionary brain-computer interface (BCI) that addresses the most pressing and costly medical needs of a rapidly aging global population, the treatment of neurodegenerative brain diseases and disorders.
NEUROSTIMULATION	DEEP BRAIN STIMULATION	REBRAIN (DBS)	FRANCE	Precise targeting technology for Deep Brain Stimulation (DBS). This is achieved through an algorithm based on Artificial Intelligence and a collaborative health data registry.
NEUROSTIMULATION	ELECTRICAL STIMULATION	SZELESTIM	AUSTRIA	innovative, patient-centred and closed-loop pain management system – AuriMod – utilizing electrical stimulation of the vagus nerve in the ear.
NEUROSTIMULATION	IMPLANTS & NEUROMODULATION	BOTTNEURO AG	SWITZERLAND	Patients suffering from chronic neuropathic pain, Alzheimer's and other neurodegenerative diseases
NEUROSTIMULATION	IMPLANTS & NEUROMODULATION	NEUROSOFT BIOELECTRONICS	SWITZERLAND	Implantable electrical interfaces
NEUROSTIMULATION	IMPLANTS & NEUROMODULATION	3DNEURO	NETHERLANDS	3D in-vivo electrophisiology. Focus on brain implants in animal models to help researchers who want to record neural activity to realize their new ideas faster and easier. Use of 3D printing and CNC machining to produce designs that combine performance, easy handling and user-centric priorities such as enabling electrode reuse.
NEUROSTIMULATION	IMPLANTS & NEUROMODULATION	NEUROCARE GROUP	GERMANY	Multipule and personalized solutions for patients with ADHD, insomnia, depression and OCD. Personalized neurofeedback is used in the treatment of ADHD, and brain stimulation (rTMS) for the treatment of depression using only evidence-based protocols.
NEUROSTIMULATION	IMPLANTS & NEUROMODULATION	ATLAS NEUROENGINEERING	BELGIUM	ATLAS Neuroengineering provides solutions for the experimental neuroscience to record and stimulate neuronal activity and offer high-density, silicon-based neural probes and peripheral. Their main know-how is silicon microfabrication, system integration, biocompatibility and histology, revolutionising in-vivo electrophysiology
NEUROSTIMULATION	NEURAL INTERFACES	INBRAIN NEUROELECTRONICS	SPAIN	Decoding brain signals into medical solutions, building neuroelectronic interfaces to cure brain disorders.
NEUROSTIMULATION	NEUROPROSTHESIS	PHOSPHOENIX BV	NETHERLANDS	Restoring/supporting vision in blind patients through a brain prosthesis

NEUROSTIMULATION	NEUROSTIMULATION	NEUROVALENS	UK	Drug-free treatments within four key health epidemics.
NEUROSTIMULATION	NEUROSTIMULATION	NEUREK	SPAIN	Transcranial Static Magnetic Field Stimulation (tSMS).
NEUROSTIMULATION	NEUROSTIMULATION	NEUROELECTRICS	SPAIN	Personalized technologies for brain monitoring and stimulation
NEUROSTIMULATION	NEUROSTIMULATION	PURE PURR	POLAND	Restoration of the autonomic regulation. As a part of complex therapy of adaptation and stress-related dysfunctions. As a part of complex rehabilitative measures, including a post-operational period
NEUROSTIMULATION	NEUROSTIMULATION	SALVIA BIOELECTRONICS	NETHERLANDS	Bioelectronic solutions that restore health for people suffering from chronic migraine. Salvia aims to provide drug-free solutions that are effective and inherently side-effect free and make the novel solutions widely accessible.
NEUROSTIMULATION	NEUROSTIMULATION	TVNS TECHNOLOGIES	GERMANY	NEMOS® is a certified medical device for the treatment of difficult-to-treat epilepsy and has been specially developed for patients who still experience seizures despite drug therapy.
NEUROSTIMULATION	NEUROSTIMULATION	OPTOCEUTICS	DENMARK	Solutions to brain health utilizing non-invasive light technologies. Alzheimer's, memory, anxiety and depression
NEUROSTIMULATION	NEUROSTIMULATION	PLATOSCIENCE	DENMARK	Evidence-based, non-invasive, neuromodulation technique for treating a range of neuropsychiatric and psychological conditions
NEUROSTIMULATION	NEUROSTIMULATION	SYNERGIA MEDICAL	BELGIUM	Chronic pain, Parkinson's disease, drug-resistant epilepsy, sleep apnoea and depression
NEW DIAGNOSIS METHODS	ACOUSTIC TECHNIQUES	CIMON MEDICAL	NORWAY	Monitoring of blood-flow in the brain of premature or critically ill infants
NEW DIAGNOSIS METHODS	ACOUSTIC TECHNIQUES	NISONIC	NORWAY	Head trauma, stroke, meningitis and other central nervous system infections, brain tumours
NEW DIAGNOSIS METHODS	ACOUSTIC TECHNIQUES	SONOCLEAR	NORWAY	Provide better ultrasound images during brain tumour surgery
NEW DIAGNOSIS METHODS	ACOUSTIC TECHNIQUES	SENSPD LTD	ISRAEL	Understanding autism and identifying a method to enable objective early detection of autism through the quest for a bio-marker.
NEW DIAGNOSIS METHODS	ACOUSTIC TECHNIQUES	SONOVUM	GERMANY	Non-invasive detection of pathological changes in the brain using ultrasound technology. Application to stroke diagnosis.
NEW DIAGNOSIS METHODS	BRAIN PRESSURE DIAGNOSIS	STATUMANU ICP	DENMARK	Detect non-visible injuries in the brain

NEW DIAGNOSIS METHODS	OCULAR DIAGNOSIS	AURA INNOVATIVE ROBOTICS	SPAIN	Parkinson's disease, parkinsonism, ataxia, dementia, cognitive, impairments and others. Evaluation of parameters to rule out comorbid conditions.
NEW DIAGNOSIS METHODS	OCULAR DIAGNOSIS	NEUS DIAGNOSTICS	SLOVENIA	Detect mild cognitive impairment
NEW DIAGNOSIS METHODS	OCULAR DIAGNOSIS	NOCTURNE	GERMANY	Detect retinal shape changes specific for neurological disorders impowered by AI
NEW DIAGNOSIS METHODS	TISSUE ANALYTICS	LUNAPHORETECH NOLOGIESSA	SWITZERLAND	Bringing –omics like approaches to in-situ tissue analytics for cancer research
NEW DIAGNOSIS METHODS	TISSUE ANALYTICS	MEDIMPRINT	FRANCE	Clinical research in brain tumours and neurodegenerative diseases
PHARMA	COMPUTATIONAL APPROACH TO DRUG DISCOVERY	GAIN THERAPEUTICS	SWITZERLAND	Lysosomal storage disorders and neurodegenerative diseases
PHARMA	DELIVERY OF DRUGS	NEUROSCIENCE INNOVATIVE TECHNOLOGIES	SPAIN	Alzheimer, Parkinson
PHARMA	MOLECULES	FREEOX	SPAIN	Stroke
PHARMA	MOLECULES	SYNDESI THERAPEUTICS	BELGIUM	Treatment of cognitive impairment
PHARMA	NEUROPHARMA	CYPRALIS	UK	Discovering and developing novel medicines for acute and chronic degenerative diseases.
PHARMA	NEUROPHARMA	KETOSWISS AG	SWITZERLAND	KetoSwiss is bringing ketones back into the modern world, especially into the life of neurological patients
PHARMA	NEUROPHARMA	NOEMA PHARMA	SWITZERLAND	Noema focuses on orphan Central nervous system (CNS) diseases characterized by imbalanced neuronal networks leading to unresolved severe symptoms and significant impact on patient's overall functioning
PHARMA	NEUROPHARMA	TOLREMO	SWITZERLAND	Develop small molecule therapies against novel regulators of drug resistance in cancer
PHARMA	NEUROPHARMA	RECEPTORPHARMA AB	SWEDEN	Alzheimer's, Parkinson's and Cancer
PHARMA	NEUROPHARMA	SINFONIA BIOTHERAPEUTICS	SWEDEN	Frontotemporal dementia (FTD) and Parkinson's disease
PHARMA	NEUROPHARMA	SINNTAXIS	SWEDEN	Discovering, developing and commercialising novel therapeutics that enhance recovery of brain functions after stroke
PHARMA	NEUROPHARMA	IMG PHARMA BIOTECH	SPAIN	Variety of full analytical services as well as development of customized tools
PHARMA	NEUROPHARMA	SAMOS MEDICAL ENTERPRISE	SPAIN	Drug for fatigue caused by neurological disorders

PHARMA	NEUROPHARMA	TARGTEX	PORTUGAL	Targeted therapies for the treatment of brain cancer
PHARMA	NEUROPHARMA	KHONDRION BV	NETHERLANDS	Damaging effects of mitochondrial dysfunction
PHARMA	NEUROPHARMA	PRIAVOID	GERMANY	Developing innovative treatment strategies based on a new class of orally available compounds.
PHARMA	NEUROPHARMA	AXOLTIS PHARMA SAS	FRANCE	Combining Preventative, Neuroprotective, Regenerative & Remodelling properties in a single drug, as the key to cure complex neurological disorders.
PHARMA	NEUROPHARMA	CERES BRAIN THERAPEUTICS	FRANCE	Treat a genetic autistic syndrome with severe intellectual delay and seizures in epileptic seizures in children
PHARMA	NEUROPHARMA	DOMAIN THERAPEUTICS	FRANCE	Advancing multiple first-in-class and best-in class programs to tackle GPCR-mediated immunosuppression in immune-oncology
PHARMA	NEUROPHARMA	INBRAIN PHARMA	FRANCE	Neurodegenerative diseases such as Parkinson's disease (PD), Alzheimer's disease (AD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS)
PHARMA	NEUROPHARMA	SEEKYO	FRANCE	New-generation cancer treatments that are able to safely transport powerful anti-cancer agents throughout the body. Targeting the tumour microenvironment and selectively release the active agent through enzyme activation.
PHARMA	NEUROPHARMA	SIGMATHERA	FRANCE	A proprietary drug that holds the potential to provide treatment for almost all neurodegenerative diseases, by successfully targeting multiple critical molecular processes involved in neurodegeneration.
PHARMA	NEUROPHARMA	PERHA PHARMA	FRANCE	Cognitive disorders associated with Down syndrome (DS) and Alzheimer’s disease (AD), and hearing loss (HL) induced by ototoxic products. A differentiating aspect with respect to other start-ups in this area is that they use marine resources for the development of drugs in the initial phases such as marine sponge or leucettamine B
PHARMA	NEUROPHARMA	DENDROGENIX	BELGIUM	Developer of drugs intended to address important medical needs in the field of neurodegenerative diseases and cancer. The company's drugs are demonstrated in vitro and in vivo for the treatment of acute myeloid leukaemia, melanoma, breast cancer and on a robust model of chemically induced deafness, enabling medical practitioners with a treatment for hearing loss and cancer.

PHARMA	NEUROPHARMA	REWIND THERAPEUTICS	BELGIUM	Novel therapeutics that block these inhibitory signals and promote effective remyelination.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	BIOINCEPTION PV T. LTD.	UK	The company develops proprietary biomarkers, drug targets and tailored diagnostic platforms. Digitise Healthcare by integrating Doctors, Diagnostics, Drugs and Data (4Ds) across a single value chain.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	KUANO	UK	The company delivers first-in-class and best-in-class drug candidates
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	MOLECULOMICS	UK	Focused on genome scale in silico modelling of protein structure, ligand docking and protein-protein interactions
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	NOVAI (DARC TECHNOLOGY)	UK	Improvement of study outcomes whilst reducing time-to-market for AMD & glaucoma therapeutics.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	CHEMALIVE	SWITZERLAND	Full and automatic calculation of accurate and reliable data for molecular properties and synthetic reactions available to all chemists from basic 2D chemical syntax.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	SIMPLICITYBIO	SWITZERLAND	Advancing clinical development—through the synthesis of diverse biological data
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	PHARMACELERA	SPAIN	The company develops proprietary Computer-Aided Drug Design software and provides access to its technology through flexible licensing options and computational chemistry services.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	MOLECULE.ONE	POLAND	Computational chemistry platform that helps bring theoretical substances to life
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	MIMESIS	ITALY	Accelerate the research and development processes
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	APPERCELL	HUNGARY	Innovative, cloud-based solution to analyse the vast amount of data recorded, and to discover new information with the help of machine learning.

PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	TURBINE.AI	HUNGARY	Simulated Cell™ integrates a digital model of cell behaviour with experimental validation and deep knowledge of translational science and molecular biology. It generates hypotheses and reveals mechanistic insights from millions of in silico experiments, getting smarter with every round, and provides end-to-end, in silico guidance, from clinical design to POC, approval, and beyond.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	BIOXPLOR	GERMANY	Aggregating the huge amounts of data generated in patient apps and clinician dashboards to extract relationships between drugs, genes, variants, pathways and patient demographics, bloods, adverse reactions and efficacy. Uses a federated cloud-based integrative platform.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	OAKLABS	GERMANY	Utilize artificial intelligence algorithms to substantially increase drug efficacy in targeted patient populations.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	AQEMIA	FRANCE	identifying or generating molecules of interest for a given project, accelerating drug discovery through in silico experiments
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	IKTOS	FRANCE	Artificial Intelligence for new drug design
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	INSILIANCE	FRANCE	False diagnosis
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	OWKIN	FRANCE	Faster development of safer and more effective therapies.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	PEACCEL	FRANCE	Positioned to be a partner of choice in AI for clients all along the continuum of drug development process, from discovery to pre-clinical and clinical trials.
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	QUBIT PHARMACEUTICALS	FRANCE	Using proprietary force fields models and molecular dynamics calculations to perform absolute free energy calculations and virtual screening, docking and visualization tools
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	SYNSIGHT	FRANCE	Innovative platform and technologies to be directly applied to RNA-protein and protein-protein interactions. Its cellular assay is unique and is able to qualify and quantify directly in human cells these challenging interactions.

PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	HAFNIUM LABS	DENMARK	Support decision making from molecular discovery to process optimization
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	MICAR21 LTD	BULGARIA	Novel blockbuster drug molecules for a large class of diseases (Pipeline).
PHARMA	NEUROPHARMA SUPPORTING & AUXILIARY METHODS	CELERIS	AUSTRIA	Alzheimer's disease and various types of cancer, like prostate and breast cancer
SURGERY	BRAIN CANCER SURGERY	HEMERION THERAPEUTICS	FRANCE	Treatment of Glioblastoma
SURGERY	EPILEPSY SURGERY	WISE	ITALY	WISE Cortical Strip (WCS) is a medical device for IntraOperative Neurophysiological Monitoring (IONM) during brain tumour and epilepsy surgeries.
SURGERY	SURGERY AND CLINICAL TRIALS AI TOOLS	PIPRA	SWITZERLAND	Reliable pre-surgical risk assessment to improve preventive measures
SURGERY	SURGERY AND CLINICAL TRIALS AI TOOLS	PREDICTHEON	SPAIN	Data Analysis, Mathematical Modelling, Predictive analytics, Personalized Medical Care, Predictive Monitoring, Pharmacologic Modelling, Physiologic Modelling, Machine Learning
SURGERY	SURGERY AND CLINICAL TRIALS AI TOOLS	NEUROMIND	NETHERLANDS	Help neurologists and neurosurgeons improve performance
SURGERY	SURGERY AND CLINICAL TRIALS AI TOOLS	DEEPTRIAL	FRANCE	Capture and monitor patient's behaviour, psychological situation (stress, wellness, etc), physiological response to drugs, quality of life (QoL), and uncover hidden insights
SURGERY	SURGICAL MICROROBOTS	ROBEAUTÉ	FRANCE	Sub-millimetric medical device designed to diagnose and treat neuropathologies. The nanobot is smaller than a human cell and can enter the brain, navigate through tissues and cells, and reach the targeted area without causing trauma, while the nanoelectronics included in the device lets it send critical information back to neuroscientists, enabling neurologists to use a device that can cross the blood-brain barrier
SURGERY	VIRTUAL REALITY FOR SURGERY	PROXIMIE	UK	Help surgeons to perform operations through a virtual room

SURGERY	VIRTUAL REALITY FOR SURGERY	AVATAR MEDICAL	FRANCE	Allows surgeons and radiologists to experience medical images in an interactive life-like environment leading to an enhanced understanding of diseases like breast cancers. It is also used in the educational sector, allowing professors to quickly import or build immersive training content to support their teaching.
VIRTUAL REALITY	E-LEARNING	INSIMU	HUNGARY	Improve diagnostic skills
VIRTUAL REALITY	GAMING AND VIRTUAL REALITY FOR BRAIN HEALTH	MIND3R	UK	Cutting edge technology combining multi sensory expertise with data from brain waves sensors to assess and manage mental health and wellbeing
VIRTUAL REALITY	GAMING AND VIRTUAL REALITY FOR BRAIN HEALTH	EODYNE SYSTEMS	SPAIN	RGS immersive virtual reality scenarios provide highly stimulating environments as compared to traditional rehabilitation settings. These virtual environments can be tailored according to the user's preferences and needs, thus motivating and maximizing training.
VIRTUAL REALITY	GAMING AND VIRTUAL REALITY FOR BRAIN HEALTH	NÓMADA OMNIMOTION	SPAIN	Treatment of motor injuries. Complete immersion in VR.
VIRTUAL REALITY	GAMING AND VIRTUAL REALITY FOR BRAIN HEALTH	SYNCVR	NETHERLANDS	Anxiety, elderly health problems
VIRTUAL REALITY	VIRTUAL REALITY PLATFORM FOR BRAIN HEALTH	HEALTH HOUSE VZW	BELGIUM	Centre to experience the impact of healthcare technology advances, based on artificial intelligence, 3D-printing, wearables, and nanotechnology solutions
VIRTUAL REALITY	GAMING AND VIRTUAL REALITY FOR BRAIN HEALTH	SYNCSENSE	DENMARK	Solve the problems related to prolonged physical inactivity and sensory deprivation
VIRTUAL REALITY	NEUROGAMES	BRAIN PLUS	DENMARK	Brain therapy on Alzheimer's disease, Parkinson's disease, depression, stroke, brain trauma, mild cognitive impairment, chronic pain, cancer.
VIRTUAL REALITY	VIRTUAL REALITY FOR PRE-INTERVENTION	HEALTHY MIND	FRANCE	Pre-operative anxiety, premedication consumption, involuntary movement
VIRTUAL REALITY	VIRTUAL REALITY FOR REHABILITATION	FOREN	SPAIN	Neurodevelopmental disorders, cranioencephalic trauma
VIRTUAL REALITY	VIRTUAL REALITY FOR REHABILITATION	LIVING BRAIN	GERMANY	Software that uses virtual reality and daily activities to treat cognitive problems in a psychologically validated, sustainable way, combined with a monitoring software for including the therapist in charge.

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Universidad Politécnica de Madrid. HBP Innovation Team

Nov 2021

Version (V.1)

UPM-2021-03

This work has been funded by the European Commission under grant 945539 (HBP SGA3) of the "Human Brain Project" (HBP) and elaborated by the Innovation Team of the Universidad Politécnica de Madrid (UPM) within the task T.8.6 of HBP SGA3.