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BLUEPRINTS ELICITATION FRAMEWORK FOR AN OPEN ACCESS PAN-EUROPEAN NEURO-IMAGING ONLINE CENTRE

Introduction. *Recent infrastructural endeavours in the field of neuroscience aimed at data integration and sharing and availability of research output. This approach recognized that opening experimental results produces significant gains for science advancement. Nonetheless, this leaves a large part of the grassroots neuroscience community underutilized: access to neuroimaging infrastructures remains locally restricted, obstructing data acquisition and the means to investigate novel hypotheses.*

Purpose. *Within our paper we seek to address this gap by providing the blueprints for a delocalized e-neuroscience centre, opening the access to functional neuroimaging acquisition systems at a pan-European level. This aim will be achieved by building operational interoperability, standardizing, and integrating the services of neuroscience centres across Europe and the development of a virtual environment allowing all European researchers to acquire state-of-the-art neuroimaging data, exploiting the principles of the European Charter for Access to Research Infrastructures*

Results. *The implementation of all necessary actions for the harmonization and interoperability of the experimental procedures of the labs entail standardization of protocols, procedures in the form of consensus-based guidelines, harmonization of hardware and software set-up and availability across laboratories, as well as adopting of common standards and formats for acquired data and metadata structures.*

Conclusion. *Consistent and streamlined mobility processes aim to become a blueprint for networking of the overall neuroscience community. The harmonized process framework presented in this paper can facilitate better use from current and future neuroscience projects. Data economies of scale and recruitment streamlining will put local EU and international funds to better use than the now dispersed efforts. This will lead to more successful projects and better pacing for EU neuroscientific communities in the international stage.*

Keywords: *multi-centre interoperability, operational harmonisation, neuroimaging, sharing infrastructures, open access framework.*

INTRODUCTION

On the side of the COVID 19 pandemic, another, a silent pandemic is harnessing Europe in the last decades: the effects of brain disorders. Europe's leading cause of disability-adjusted life years (DALYs) is the effect of the central nervous system and brain disorders [1]. Yet, Europe has yet to develop a pan-European strategy that would respond effectively and decrease brain disorders' effect on reducing the quality of life. A horizontal approach cannot succeed due to the great diversity in brain disorders' manifestation and treatment across the different European regions [2]. Inter-regional differences in disorder manifestation that drive the corresponding inter-regional variability in brain disorder DALYs are unknown. The current infrastructural paradigm in functional neuroimaging, which grounds on the existence of a variety of distributed and independent centres, as well as equipped they are, cannot respond to the need: their experimental procedures and results are independent and incomparable. Only a pan-European neuroimaging centre that can run at an open access basis, the same procedures across different European Union (EU) regions simultaneously and generate validly harmonized results can identify the drivers of inter-regional variability in brain disorder manifestation.

PURPOSE

To develop detailed models of brain disorders' effects, incorporating data regarding inter-regional differences that can inform regional defined interventions and pan-European strategies which aim to reduce the disorder's systemic effects, the current research attempts to provide the rational towards a pan-European, decentralized, open and expandable infrastructure for transforming the ability to fight brain disease and understand brain health by incorporating inter-regional confounds of neurological disorder manifestation through a methodological and technological infrastructural harmonization. Grounded on the harmonization of existing infrastructures and processes our framework intends to exploit the notion that "the whole is greater than the sum of its parts".

PROBLEM STATEMENT AND AREAS OF CONSIDERATION

Background on interregional variability in brain disorders state of the art (S.O.T.A.)

Brain disorders are one of the greatest health challenges. Around 165 million Europeans are living with a brain disorder. European healthcare budgets are burdened by €800 billion per year, and this is expected to increase further as Europe's population ages and becomes more susceptible to brain disorders. Importantly, brain disorders and their effects show great inter-regional variability: some level of commonality in the prevalence of certain disorders exists, but a significant diversity in their manifestation and treatment across European regions results in a great diversity of their effects, as reflected in the inter-regional variance of disability-adjusted life years (DALYs) [1]. The rate of people in the world who die or are disabled from Alzheimer's and other dementias (which show the greatest increase over the last 25 years) ranges from 1109 DALYs per 100000 in Italy to 409 in Cyprus [3].

As far as ease-of-access is concerned, neuroimaging infrastructures that are remotely interlinked offer the opportunity for ease of access services that cover very specific needs of the researchers that will use them. Telepresence infrastructures like a mixed reality teleconferencing component are not unheard of in the healthcare sector and have been implemented in surgery teleconsultations amongst other uses. Remote operation of medical devices has been implemented numerous times in the context of telemedicine and can be readily implemented within the scope of the proposed infrastructure, supporting specificity in experimental execution. Focusing on the rigor that is required in neuroscientific experiments, an experimental protocol verifier tool has and can be implemented, that would consider the specifics of the equipment at hand, correcting or rejecting remote research protocols that are misaligned or unfeasible in the context of the infrastructure. Additionally, data pre-processing services or full processing services are within the scope of this infrastructure's ease of use and research usefulness suites. Furthermore, educational resources in the form of educational videos, online manuals, and knowledge base portals are staples in the support suite of every neuroimaging device and are provided as standard by their vendors.

FRAMEWORK DESCRIPTION

The inter-regional diversification of the DALYs of brain disorders in the population has been recently documented, but this does not stand also for the different disorder features. Our framework intends to allow the documentation of the disorder manifestation characteristics that drive inter-regional variability. Infrastructure modalities are needed as potentially standardized and harmonized means of intervention. Without knowing the elements that drive the differential effects of brain disorders inter-regionally, Europe cannot build a stable strategy to reduce the disease burden in a changing society. This goal falls beyond the scope and resources of any single country and must be addressed collectively. Up until now, the lack of resources and infrastructure for defining the inter-regional characteristics of brain disorders manifestation, has hampered progress in understanding the disease burden and improving brain health. The infrastructure needed for such an endeavour is grounded upon better coordination of research among European countries and beyond, as well as between academia and industry (i.e., science diplomacy).

The characteristics of such infrastructure include a decentralized structure that integrates functional neuroimaging hardware, processes, and analyses in such a way that interregional variation of neurological disorders can be studied directly at a pan-European level. Integrating different neuroimaging modalities, such as MEG, EEG, fMRI, and complemented by brain activity modulation techniques such as TMS and tDCS, this kind of structure will be able to achieve the full potential of methodological complementarity. Hence, a structure with procedural and technological infrastructural harmonization that operates inter-regionally and can be utilized by the European research community, to produce comparable results. This will then allow answering the scientific challenge of modelling the manifestation characteristics that drive the inter-regional diversity of DALYs.

The technical composition of such an infrastructure can be rather specific given the neuroscientific equipment (e.g., MEG, EEG, MRI, TMS, tDCS amongst others) involved. However, the specificity of data and equipment integration (e.g., stimulus synchronized MEG-EEG recordings, post tDCS EEGs, etc.) is always defined by the neuroscientific question. In that context, the case-by-case needs analysis is the framework that informs the specific infrastructural modalities that will be utilized in each case as well as their data integration and processing methodology. A questionnaire with closed answers can be created and disseminated among European scientists focusing on interregional variabilities of brain disorders. Such a questionnaire can be disseminated from social media, conferences, and networks of scientists/stakeholders in which the partners participate, reaching a wider acceptance and including questions that will define typical experimental paradigms and neuroimaging modalities needed by the community. The data gathered can then be analysed using descriptive statistics to ground the decisions of formatting our framework's structure.

While the ease of access provisions is not possible, nor desirable to be integrated into the proposed concept infrastructure, our framework aims to engage in a comprehensive participatory approach to involve the neuroscientific community in the process of selecting the most impactful and appropriate features for ease of access. A series of co-creation sessions will touch on every aspect described above. Thematic distribution in different sessions will ensure that clarity of purpose will be maintained. Agile principles will be transferred from IT to this needs analysis to streamline the participatory process. Engaging the full range of stakeholder target groups, user stories, personas and other established workflows of participatory UI design will be used in the co-creation sessions that will take place. The transnational dimension of stakeholder engagement will be maintained through the heavy use of teleconferencing and collaborative tools like interactive storyboards (e.g., Miro board). This process will identify the best impact/cost ease of access features that will empower the concept infrastructure.

Generally, in the context of every neuroscience research case there are already defined constitute parts that define and designate it as such. These include the core research question, which serves as the defining anchor of the research use case. Defined by this, but equally constant as a constituent part, is the equipment and methodology of the experimental setup for the use case. Equally important in the definition of every neuroscientific research use case are the necessary pre-processing and algorithmic processing approaches and the interplay of them with the data integration that is required from the relevant infrastructure. Also, as in every use case, experimental cohort composition as well as inclusion and exclusion criteria are also important constituent parts of every rigorous neuroscientific research use case. These use case features cannot, however be arbitrarily assessed against the overall scientific challenge of interregional differences of brain disorders.

Our framework intends to become more than a technical infrastructure for researching interregional brain disorder differences. As such, in the framework's recommendations for upscaling of the infrastructure there is the provision of identifying the field's major research axes. Through that endeavour our framework intends to formulate an authoritative, continuously updated knowledge base that will be able to identify the relevance of neuroscientific research cases within the specific field.

AN INNOVATIVE INTERPRETATIONAL MODEL

Multilayer modelling of interactions between brain functionality, cognition/behaviour, quality of life/dalys, and regional characteristics of health systems

The neuroimaging, behavioural, quality of life, and societal data can subsequently be incorporated in a multilayer network model, with brain functionality, cognition/behaviour, quality of life/DALYs, and regional characteristics of health systems as different layers. Taking advantage of the latest advancements in complex network science that led to the extension of graph analysis to the modelling of multilayer representations consisting of distinct networks [4], this network model will allow the detailed quantification of the interactions amongst those layers that drive inter-regional differences. This allows the modelling of global functional connectivity characteristics between the layers of the corresponding hypernetwork. As such, it has the potential to evolve our current two-dimensional understanding of the link between neurobiological deficits and DALYs into a multi-layered construct that effectively interprets the complexity of this relationship.

The challenge of merging connectivity metrics amongst the different disciplines will be overcome by estimating hyperedges that depict the interaction between nodes of the functionally distinct network layers in the graph [5]. Each measurement (i.e., brain functionality, cognition/behaviour, quality of life/DALYs, and regional characteristics of health systems) will constitute a distinct layer. Within-layer nodes depict the manifestation of the disorder in the corresponding layer, and their interaction pattern is modelled by a connectivity analysis that utilizes metrics dictated by the consequent discipline. Normalization will be applied to homogenize the networks across all layers and render them comparable to each other. Between-layer co-occurrence of the deficits will model the node-to-node interaction amongst different domains: The profiling of the co-occurring problems will be carried out using Spearman's rho and its output will attribute each node pair with a weight based on the co-occurrence of the corresponding symptoms. The corresponding hypernetwork of each individual will then be subjected to a statistical evaluation based on general linear modelling, like the one shown in [6]. Global network characteristics (e.g., resilience or topological characteristics such as clustering persistence diagram), appropriate for multilayer networks can also be estimated as indicators of the overall structure of the network. The structure of the model, having free weights on each node will be proposed as a template interpretational tool for later studies aiming to understand how other brain disorders affect the corresponding interregional DALYs variability.

Tackling global health challenges such as dementia has been directed toward the development of affordable, scalable, and broadly available biomarkers of brain connectivity [7]. Over the last two decades, M/EEG studies have benefited from the increased sophistication of processing pipelines, allowing researchers to gain more insight into the dynamics and connectivity of the brain [8]. This is illustrated by recent M/EEG studies incorporating graph theory, nonlinear dynamics, decoding, and whole-brain modelling, which bring novel opportunities for the study of dementia [9], [10].

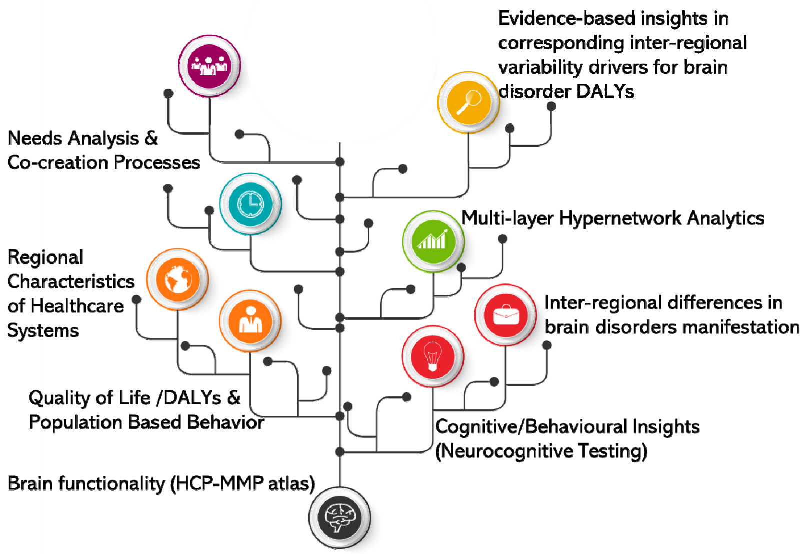

Fig. 1. Bird's Eye View of the Proposed Framework

The proposed approach based on the analysis of large volumes of standardized and harmonized data is expected to increase the efficacy of diagnostic tools and intervention strategies. Though the current and potential impact of functional connectivity studies based on M/EEG cannot be ignored, developing M/EEG multicentric studies is not an easy road and involves major technical difficulties and organizational needs. For instance, in a typical multicentric approach to task-related M/EEG functional connectivity, the major drawbacks arise from the task design, which needs careful validation. Furthermore, typical multicentric studies involving the acquisition of task-related M/EEG face several technical challenges, which include compensations for different stimulation timing and M/EEG synchronization procedures.

The framework therefore will consist of: (a) Acquisition protocol & Environmental settings and data quality measures, (b) Data sharing procedures, (c) basic pre-processing, (d) advanced pre-processing, and (e) a multilayer framework for M/EEG connectivity. Standardization and harmonization applied within the framework workflow will include: (i) a harmonization of M/EEG measurements to attenuate any variability linked to lightning, acoustic background noise, electromagnetic noise of the M/EEG chamber and other setting conditions, but also between resting-state (eyes-open and eyes-closed) measurements i.e., room lighting, and ERP measurements i.e., compensation of time delays, synchronization procedures, (ii) a standardization for data sharing i.e., following organizational standards for data sharing and applying an annotation and classification system, (iii) a standardization of basic and advanced pre-processing steps such as re-referencing, filtering, rejecting bad channels and bad segments, artifact rejection, etc, leading to spatial harmonization, data normalization of data from healthy participants as well as patient-control normalization and (iv) the estimation of a multilayer network of each patient phenotype.

An important step in M/EEG harmonization will be the measure of the harmonization success an essential element for guiding further data analyses and planning future preclinical studies. Such measures will consider the acquisition system and relevant acquisition parameters as covariates in the framework M/EEG studies of connectivity. Acquisition systems can make a significant contribution to the variance of multisite M/EEG studies, particularly when they differ in the type of electrodes/sensors, and electronics. Metrics indicating the success of the harmonization will refer to source space and will help to build methodological consensus, which in turn will contribute to establishing functional connectivity measures as reliable biomarkers for the early identification of subtypes within a particular neurodegenerative disorder and facilitate intervention. This early identification system implies that the traditional classification of neurodegenerative disorder based on group analyses shall be complemented with individual-level analyses. Finally, the methodology for sharing data and its ready-to-use processing pipelines will be critical for the replicability and cross-validation of the framework studies.

Development of a horizontal interconnection of the labs in terms of infrastructure operation. Currently, the operation of each infrastructure is executed via direct commands on the manufacturer's software defining the corresponding measurement parameter. The different software uses similar but not identical names for each command while the user interface is diversified in accordance to the manufacturer's style. This ensures operability from each lab's technician or operator but obstructs the option of one operator knowing and acting at several systems. The suggested framework intends to ground its horizontal interconnection on a system consisting of (a) a Sandboxed Data Container, (b) an authentication system, (c) an SDK handling communication with different manufacturers' operating system of each infrastructure and (d) a General User Interface (GUI) operated digital twin of a simplified version of manufacturer's software. Specifically, it will develop digital twins of each software, running at a Sandboxed Data Container (SDC), ensuring safety of the system. The digital twin of each software will have a simplified General User Interface, and commands that are to be utilized for fine-tuning the parameters of experimental paradigms. This deadlock is one of the core aspects that SDC tries to overcome through by-design mechanisms where the data, processes, metadata, and the intermediate results are safeguarded and protected by any unauthorized entity (Event Handler tier). Software commands which are not to be handled by external operators (for system's stability and safety reasons) will not be visible and will remain functional only in the original software of the system manufacturer. These features can cover the aspects of privacy and security, so the SDC can ensure to the data owners that their data is secured and monitored (Monitoring tier) in a way that no one else can intervene. The names of the commands that are to be used will be unified across the labs.

In more detail, the instantiated SDC includes the researcher's credentials, which are used by an Authentication Server (AS) to grant the access. Hence, when an external operator of the virtual infrastructure (after receiving relevant permission and login info from the common user interaction gate) enters the system as operator, s/he will see a unified user interface independently of the system, with common names on each parameter to be operated. Inside the SDC realm, each data is handled as a unique entity and is governed (Data Service & Storage tier) with different constraints and regulations. This is the case of interest for many scenarios since each person must have the freedom to define personalized policies of his/her own data. This approach will allow experienced experimenters (after a short virtual educational seminar on operation of the unified system) to be able to handle all infrastructure operation that will be used for recording of the corresponding experimental paradigm, while maintaining system's stability. The corresponding commands will be sent to the original software to run the analogous functionality. One key principle that the system will cover is the adherence to the different policies used by each hospital or institute on data management rights. Important points of this approach are (a) the sandbox's operation, (b) the homogeneity of GUI of the digital twins of all different software, (c) the choice of the parameters and operation commands that will be available to external – virtual users. The later will have to be defined in relation to decisions made based on the experimental paradigms that will be offered, as well as on the basis of system's stability.

Development of a vertical interconnection of the labs and common user interaction gate in terms of infrastructure operation. In line with the overall objective of unifying data and processes from individual laboratories in the neuroimaging domain, the framework should be supported technically by a scalable infrastructure and a set of data handling tools. The infrastructure will receive data from the individual laboratories and will apply data quality analysis, anonymisation and transformation to provide them to the researchers upon relevant requests. Moreover, a two-way communication link between the researchers and the labs will be established to allow conducting experiments based on specific protocols. The architectural overview of the technical infrastructure is shown in the Figure 2.

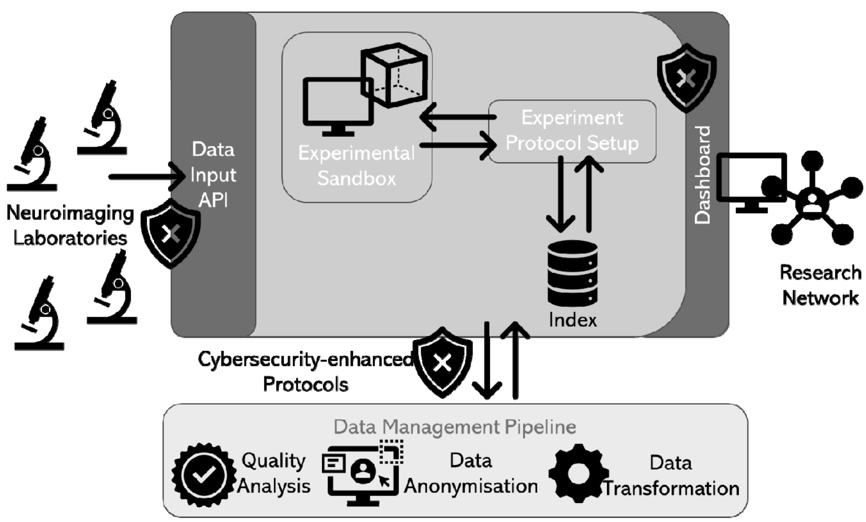

Fig. 2. Architectural Overview of the Framework's Technical Infrastructure

The infrastructure comprises a data input API built in REST so that it allows implementing different connectors for the data and experiments of each laboratory. The input will be inserted based on an event streaming platform, such as Apache Kafka, to ensure high throughput and high availability. The system will also involve a data management pipeline so that the data are initially analyzed and anonymized, ensuring that any sensitive identifiable information is not forwarded to the user. Furthermore, data transformation will be supported in order to produce an output format that will be suitable for data presentation/visualization to the researchers.

The core component of the infrastructure is the communication layer, which will be used to conduct and retrieve experiments performed in different laboratories. From the perspective of the researcher, an experiment dashboard will be used as a unified environment that allows exploring the data and equipment availability of the different labs. The researcher will be able to upload a new experiment request via an intuitive UI, using an appropriate protocol for the experiment. All experiments, along with the relevant protocols will be stored in a searchable index, allowing easy retrieval. This way it will be possible to check whether new experiments are compliant with existing protocols and/or provide recommendations based on AI to make them compliant.

Upon determining a relevant lab, in terms of data and availability, the researcher will be able to run the experiment in a virtual sandbox. The sandbox is built using virtualization technologies (e.g., Docker), ensuring that the laboratory data are secure from potential compromises, either intentional or not. State-of-the-art security protocols will be used to connect to virtual instances of the sandbox. The data produced by the submitted experiment will be forwarded to the data management pipeline. The pipeline will initially perform quality checks, focusing on curating (pre-processing is performed in the labs). After that, the data will be anonymized using state-of-the-art anonymization techniques to ensure that all valuable information is maintained while removing any personally identifiable information. The final step will be that of data transformation. The researcher will have control over the format of the data and will be able to request for different statistics and/or visualizations. The results of the system will be presented to the users in a dashboard, while they will also be available using a RESTful API. Therefore, several visualizations will be available to aid the interacting parties in understanding the output and providing useful suggestions. Focus will be given on statistics and data aggregation techniques, while full data retrieving as streams will also be supported.

Secure data movement techniques. Protecting data, either in transit or at rest, is a necessity that plays a catalytic role, especially in cloud computing infrastructures. The most basic countermeasure that ensures data privacy are properly configured access control policies. Discretionary Access Control (DAC), Mandatory Access Control (MAC), Role-Based Access Control (RBAC) and Attribute-Based Access Control (ABAC) are some approaches. However, these do not provide absolute security, and sensitive data might still get exposed in case of attacks, especially during the data transmission between source and destination (e.g., man-in-the-middle attacks). In all cases, data encryption by the data owner before it is uploaded to the cloud is necessary; in this way confidentiality is guaranteed even in case of breaches and leaks.

However, classic encryption techniques, such as Advanced Encryption Standard (AES), Data Encryption Standard (DES), and Triple Advanced Encryption Standard (3DES), are not feasible in cloud computing settings due to their complexity and lack of flexibility, scalability, and fine-grained access control [11], [12]. Instead, cloud-suitable alternatives are Attribute Based Encryption (ABE) and Identity Based Encryption (IBE). Traditional encryption mechanisms involve the data owner encrypting the data with a user's public key before uploading them. The user can then decrypt the data using their private key. In IBE, public keys are calculated based on a unique identifier of a user, such us their e-mail address. This eliminates the need of public key retrieval [13]. The private key is distributed by a private key generator. ABE (also known as fuzzy identity encryption) uses a combination user attributes instead, such as their name, city, or street number to generate public/private keys [14]. In addition to data confidentiality, data integrity is another critical element in data security. Data integrity refers to protecting data from unwanted modification, deletion, or fabrication. The first step in ensuring it, is proper access control through authorization. In addition, RAID strategies store data in different locations to provide redundancy and fault tolerance [15].

Finally, Data Integrity Validation (DIV) techniques provide assurance to users that data is intact and has not undergone corruption, deletion or modification. RSA and MD5 are some of the simplest techniques, where downloaded data signatures are calculated and compared to a reference. In addition to these, public auditing techniques offer a scalable alternative, where a Third-Party Auditor (TPA) is introduced to handle the interaction with the Cloud Storage Server [16]. Finally, where preventive measures fail, timely detection of the failure is necessary. Intrusion Detection Systems (IDS) monitor an infrastructure at the network or file-system level for abnormal behaviour as well as unauthorized data access [17]. These, in turn, can trigger appropriate mitigation actions, such as Moving Target Defenses (MTD) which can significantly increase an attacker's uncertainty and decrease their chance of success [18].

Co-creative iteration on all components. Co-creation as a part of the field of participatory design has received significant attention in the context of innovation in recent years. Due to the efficiency and adaptability in responding to diverse and changing environments and contexts, this has been identified as a potential booster for the implementation of innovative and experimental solutions [19]. The main point of co-creation is the transformation of passive actors such as end-users into active ones. Hence, they are actively involved in the development processes of products, services and systems [20] as well as the definition and creation of common values taking all actors and their needs into account [21]. Users and actors are not considered just during research process in co-creation methodology, but also throughout the production phases such as inspiration, co-design, testing, and execution of a solution. This includes the co-production process [22]. From a business point of view, this active participation in co-creation processes usually aims to shift the focus from a business centric one towards personalized and satisfying customer experiences [23]. These characteristics of co-creation methodology and its value led to expanding the fields of application as well as the notion of concept. More specifically, it has been attempted as a promising means to engage neglected actors and stakeholders in various domains of innovation (e.g., in public sector innovation) and as a way to set up collaborative processes like those that are needed to better involve in innovation [24].

Our framework intends to guide pilots which should be accommodated by the infrastructure-driven partners, intrinsically adopting the co-creation methodology as its principal objective. This refers to a systematic user co-creation approach integrating research and innovation processes in real life communities and settings. In practice, the exploitation of qualitative and quantitative data of the needs analysis can shape the plan of integration and harmonization of the infrastructure and services as well as the configuration of the blueprint that will depict the vertical infrastructure, subserving the common gate of experimental protocol and user interaction. In the following, those plans will be forwarded via a second iteration of questionnaire dissemination and feedback sessions addressed to a shorter list of scientists of the ERA that focus on inter-regional brain differences and relevant targeted stakeholders. As such this process will employ co-creative elements in an iterative feedback process that will align the concept of the infrastructure and its implementational details.

Blueprints for Infrastructure scaling up and processes generalization Technical Scale-up Blueprint. Current infrastructural paradigm of functional neuroimaging relies rely on various distributed and independent centres, that cannot serve the necessity for experimental procedures and results to be relevant and comparable. An increasingly high cost of acquiring and maintaining a neuroimaging facility offering all modalities, restricts the availability of such resources at a European level. Hence, the local access to neuroscientific infrastructures offering high-quality neuroimaging services for all imaging modalities provided by the framework is currently uncommon across the European area, restricting the full use of the operational time of the corresponding infrastructures (several such infrastructures currently have free operational time, as their use is based on experimenters performed from a small number of researchers), and the exploitation of the scientific knowledge and expertise of researchers which do not have access to such infrastructure. Therefore, the framework's goal is to create the ground for a modular system that will be able not only to integrate the different infrastructure horizontally, but also to support the whole variability of experimental needs of the ERA scientists focusing on inter-regional variability of brain disorders. Hence, a modular system that will be utilizable for different experimental use cases. Thus, a set of operations and services that are needed to answer the community's needs will be defined and a modular system will be described in detail that will be able to implement the different experimental procedures across the different labs. Hence, a system that will not only include in the sandboxed operated digital twin, the software commands that are needed to run the resting state analysis of defining Subjective Cognitive Decline manifestation, but also all the software commands that are needed to run all the experiments defined by the community via the needs analysis. Technical requirements that are needed for a new infrastructure's operating system to integrate to the framework system and to connect to the corresponding SDK will be defined and published accordingly. Scientific and methodological requirements regarding the services and the lab's support for the system to run fluently will be defined, comprising of best practices for each neuroimaging facility.

Alongside, a common technical framework for compiling novel use case scenarios, novel experimental paradigms and research protocols will be defined.

This will include global definition of terms, so that a common set of procedures is easy to define across labs, and a definition of neuroimaging modalities used under the umbrella of the framework canvas so that that the protocol is easily evaluated on the basis of the functionality of the integrated system. A template protocol allowing specific definitions on the parameters (the ones applicable on the integrated framework system of the infrastructure) will be prepared while initially, an algorithm will evaluate applicability of the protocol in the integrated system. At a second stage a technician/researcher of, familiar with the functionality of the integrated framework system will evaluate further details. As soon as this two-stage procedure is completed, and the common technical framework of a newly submitted experimental protocol is respected, the research will be prioritized for implementation. These elements will comprise the technical blueprint of upscaling the number and variability of infrastructure included, allowing integration of other European labs in the common functionality of the virtual decentralized system.

Scientific Diversification Blueprint. Several brain imaging projects have attempted to identify suitable biomarkers of neurodegenerative disease. For instance, the Alzheimer's Disease Neuroimaging Initiative (ADNI) contributed to the development of blood and imaging biomarkers, the understanding of the biology and pathology of aging, and to date has resulted in over 1800 publications. ADNI also impacted worldwide ADNI-like programs in many countries worldwide. Though, these previous mega-studies have contributed to the discovery of potential mechanisms and biomarkers of multiple brain disorders, most of these imaging biomarkers have a relatively small effect sizes and the study results were drawn from multi-site data which are often heterogenous and used now outdated traditional low-resolution data acquisition protocols. In addition, there have been no human brain M/EEG studies that explore multiple neurological disorders that occur through the lifespan within the same cohort of subjects. Currently, typical multi-site studies for studying brain disorders have great advantages such as: (i) quicker recruitment of the necessary number of subjects, (ii) clearer results as the patient sample of multi-site trials is supposed to be representative and can potentially reach for more generalizable findings, (iii) sharing resources amongst collaborative sites, and (iv) promoting networking. However, multi-site trials require strong efforts for quality assurance concerning admission, treatment and follow-up, thus a highly developed coordinating centre is needed. In addition, typical multi-site neuroimaging studies have been based on a single or small number of the same model M/EEG systems at different sites and thus did not fully address standardization of the data acquisition across different scanner models or vendors. In addition, such studies usually require the procurement and/or distribution of common neuroimaging (e.g., portable EEG systems) devices of same specifications to attenuate the variability in the expected results. However, this practice can significantly increase the cost of such studies, while it can introduce errors even in the acquisition phase as the researchers of a centre may not be entirely familiar with the newly operated devices. In line with this, this practice likely excludes the use of MEG systems if sites haven't procured in the past as the systems require a dedicated space for installation, and cost from €1.5–4 million.

Our framework aims to accelerate harmonization technologies to be used in the integrated neuroimaging centres by combining approaches to high-quality imaging acquisition, pre-processing, study design, and statistical bias correction to potentially improve the sensitivity and validity of imaging results. The conceptual framework for major health challenges will be based on the notion that as patients are not the same, regions are not the same, thus it will follow a population centred approach and take into account differences of the EU society compared to the available literature, metanalyses, clinical trials and guidelines. These observed differences will improve understanding of disease pathophysiology and help researchers to tailor their approach and research questions based on the population characteristics. All use case scenarios that address global inter-regional health challenges will be introduced into the relevant ecosystem via a common scientific framework. This will include forming hypotheses regarding the Impact of inter-regional differences in each health challenges and thus forming appropriate research questions that can account for account inter-regional differences. A unified template protocol will set the use cases' endpoints which will include features and measures derived from the imaging modalities and will provide a benchmark against which other phenotypical data will be assessed. These endpoints will provide objective evidence of beneficial and adverse outcomes.

Though aims will differ across the use cases, the framework will drive the main endpoints but also serve as an exploratory tool that contributes to the understanding of disease mechanisms. Studies under the framework's umbrella are a response to the increasing demand for more data, but can also promote collaborations across institutions and countries, and experts worldwide will have access to the large data sets and can combine their group expertise. Thus, a framework for new data syntheses will be defined, ensuring that appropriate technologies and strategies are used to manage the large amounts of data generated.

Policy upscaling Blueprint (Developing a unified financial, administrative, and regulatory framework exemplar for EU multicentric Research and Innovation). The unified financial, administrative, and regulatory framework exemplar for EU multicentric Research and Innovation pertains to regulatory issues and problems related to Copyright and Data Protection in the field of Research and Innovation which may be resolved in a way that allows for successful administrative and financial planning. Regarding Copyright law regulatory issues, we assess that the proposed framework's successful operation depends on the exploitation through the Internet of information goods and/or databases of information goods which will be distributed Europe-wide. The excludability imposed by Copyright's legal edifice to said information goods and databases is a regulatory issue to cope with through Openness in Copyright law and the new mandatory exceptions and limitations introduced through Directive 2019/790/EU.

In addition to Copyright law issues, planning entails the successful handling of data protection issues. The envisioned framework should have to cope with proper action for the implementation of the General Data Protection Regulation's mandates, i.e., Regulation 2016/679/EU. Therefore, personal data protection considerations will also have to be assessed carefully. The GDPR must be considered in relation to the suggested setup and operation from a viewpoint that meets the requirements of the adoption of privacy-by-design and advanced security techniques. GDPR compliance is a task related to internet security of the infrastructure of it, thus compliance with the requirements of Directive 2016/1148/EU concerning measures for a high common level of security of network and information systems across the Union as well as the acquisition of proper European Cybersecurity Certification provisioned in Regulation 2019/881/EU could be considered.

Most likely ethical issues will be faced, too, at least in the sense of drawing up and/or imposing a code of conduct for scientific research and innovation. For example, ethical restrictions imposed by Regulation 2014/536/EU and the Principles of European Medical Ethics adopted by the European Council of Medical Orders on 06/01/1987 including the principles adopted on 06/02/1995 or the ethical principles adopted in Kos Island (Greece) of the European Charter of Medical Ethics in 10/06/2011 will have to be considered.

In addition to the regulatory framework as outlined above, the new infrastructure should define prioritization algorithms based on excellence for admitting new protocols/studies from all ERA scientists, working as an open access infrastructure. The algorithm will define in detail, which research protocols are undertaken by the new infrastructure, which are prioritized over other in case that more than one is submitted, how the work is distributed across the partners, and under which regulations performing the study will be realized.

CONCLUSION

The current paper presents a pan-European functional neuroimaging framework, that will be able to model inter-regional differences in brain disorder manifestation. The suggested framework will rely on the principles of open science, offering its services and high-end decentralized infrastructures via virtual access to all European scientists based on an "access through excellence" gate. Expanding on the opening of science via the first (i.e., open access papers) and second (open data) pillar, the pan-European centre will open access to the third pillar of science: infrastructure. It will include the means and procedures to perform state-of- the-art experimental protocols proposed by the community of European neuroscientists targeting inter-regional differences for a variety of brain disorders.

In order for the framework to be developed it will require a horizontal harmonization of infrastructures and standardization of procedures by a decentralized set of state-of-the-art laboratories guaranteeing validity and comparability of research results obtained from a variety of labs participating across different European regions. It should also have a unique and common virtual access gate for all integrated labs and all European scientists aiming to utilize its services offering a simple, yet a user-friendly way for each scientist to submit a research protocol that will be able to run inter-regionally. Thus, it will offer its services via remote access incorporating digital twins of all systems in the cloud, and thereby allow the running of experiments simultaneously in the different labs, without the physical presence of the researcher in all of them.

The suggested framework is designed so as to offer the possibility to every neuroscience centre across Europe to participate as a hub of the pan-European structure following guidelines and procedures of integration. It defines a novel organizational model operating as a unique but decentralized structure of integrated working hubs, able to pool and share resources in studying inter-regional differences in brain disorders manifestation. Built upon a set of "small-world" network properties, the framework allows the functional integration of highly specialized research hubs into a working virtual neuroscience over-structure.

Finally, we present the blueprints of a unified financial, administrative and regulatory framework exemplar for EU multicentric Research and Innovation pertains to the regulatory issue. Following ESFRI principles and drawing upon similar structures such as the Synergies for Europe's Research Infrastructures in the Social Sciences (SERISS), the framewok defines procedures to accept the implementation of research protocols submitted openly by the community. Moreover, it defines the prioritization of studies submitted, means of financial compensation of the hubs for executing the research and accountability. The opening of infrastructures and procedures via pre-defined principles will answer the risk of fragmentation of funding after the end of some of the large-scale programs in 2023 and systematically align the research agendas to a synergistic commitment. Overall, it will define actions related to copyright law issues, data protection, cybersecurity, ethical and contract/business issues as a pan-European structure. The blueprint will also define ways of collaboration, research refinement, and complementarity with other major initiatives in the EU (EBRI, EBRAINS, the JPND joint program, the Human Brain Project) and across (Brain Initiative) that will allow means of exchange and implementation of interregional research services.

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ПЛАТФОРМА ВИЯВЛЕННЯ СТРУКТУРИ ДЛЯ ЗАГАЛЬНОЄВРОПЕЙСЬКОГО ОНЛАЙН-ЦЕНТРУ НЕЙРОВІЗУАЛІЗАЦІЇ З ВІДКРИТИМ ДОСТУПОМ

Вступ. Нещодавні інфраструктурні зусилля в галузі нейронаук було спрямовано на інтеграцію та обмін даними та доступність результатів досліджень. Цей підхід визнав, що відкриття експериментальних результатів дає значні переваги для прогресу науки. Тим не менш, це залишає значну частину масової нейронаукової спільноти недостатньо інформаційно забезпеченою: доступ до інфраструктури нейровізуалізації залишається локально обмеженим, що перешкоджає збиранню даних і використанню засобів для дослідження нових гіпотез.

Метою статті є прагнення усунути цю прогалину, надавши платформу для делокалізованого центру електронної нейронауки, що відкриває доступ до функціональних систем нейровізуалізації на загальноєвропейському рівні. Ця мета буде досягнута шляхом побудови оперативної сумісності, стандартизації та інтеграції послуг нейронаукових центрів по всій Європі та розроблення віртуального середовища, що дасть змогу всім європейським дослідникам отримувати найсучасніші дані нейровізуалізації, використовуючи принципи Європейської Хартії доступу до дослідницьких інфраструктур.

Результати. Реалізація комплексу необхідних дій для гармонізації та забезпечення сумісності експериментальних процедур різних лабораторій передбачає стандартизацію протоколів, процедур у формі настанов на основі консенсусу, гармонізацію налаштувань апаратного та програмного забезпечення та доступності в лабораторіях, а також прийняття спільних стандартів і форматів для отриманих даних і структур метаданих.

Висновок. Послідовні та впорядковані процеси мобільності мають за мету стати структурою для створення мережі спільноти нейронауковців у цілому. Узгоджена структура процесу, подана у такому документі, може сприяти кращому використанню поточних і майбутніх проектів нейронауки. Економія даних за рахунок масштабування створених програмних продуктів та оптимізація впорядкування надасть можливість використовувати місцеві кошти ЄС і міжнародні кошти краще, ніж нині у разі розпорошених зусиль. Це приведе до успішніших проектів і кращого темпу поповнення вагомими результатами нейронаукових спільнот ЄС на міжнародній арені.

Ключові слова: *багатоцентрова сумісність, оперативна гармонізація, нейровізуалізація, інфраструктури спільного використання, структура відкритого доступу.*