The Neuroscience Research Cluster
for the investigation of psychiatric disorders

In vivo neuroimaging techniques have made huge progress over the last decades and opened up central access to the understanding of neural communication and of mental processes in general, both, of the healthy and diseased brain. Given the technical progress, multimodal brain imaging is a resourceful development which provides fingerprints of hemodynamic, metabolic and electrophysiological activity in the living human brain in such a way that structural, functional, and molecular information is recorded in synchrony [1]. With the recent development of devices combining positron emission tomography (PET) and magnetic resonance imaging (MRI), magnetoencephalography (MEG) and electro-encephalography (EEG) or MRI-EEG/PET-MRI-EEG, the field achieved a step of paramount importance towards understanding the neural mechanisms in psychiatric disorders, such as major depressive disorder (MDD) has been made. The direct and indirect costs of psychiatric and neurological disorders pose a high burden on the patients, their families and nations around the world. Paul Summergrad highlights this in his recent editorial by stressing the fact that the return of investment in mental health is 2-3Euro per invested 1 Euro [2]. The Neuroscience Research Cluster with its highly interdisciplinary approach integrating physicians, engineers, physicists is ideally positioned to contribute in tackling this challenge.

Aims

This proposal aims at integrating and linking existing Palestinian-German collaborations and expertise to foster a solid neuroscience research platform. Through this proposal, we will build and expand new infrastructure for research on psychiatric disorders in both Palestine and Germany. This will complement ongoing research in neuroimaging, cognitive neuroscience, and genetics research in both Palestine and Germany. Further, this will facilitate future studies utilizing new research methodologies to explore the cognitive, physiological, and genetic determinants in healthy individuals and patients with psychiatric disorders. We will utilize novel approaches in neuroscience and advanced data analysis. In particular, the creation of this research cluster aims to achieve the following specific objectives:

- Integrate expertise in neuroscience research on the Palestinian and German sides. In particular, we will bring together experts in machine learning, neuroimaging, neurogenetics, cognitive neuroscience, computational neuroscience, and neurophysiology. We will capitalize on existing overlaps in expertise and complement.
- Build infrastructure for neuroscience research in Palestine by securing training opportunities for Palestinian researchers at the Forschungszentrum Jülich and RWTH Aachen and investing in equipping research labs in Palestine to conduct imaging research.
- Conduct high-impact multidisciplinary research that combines various expertise and data from imaging, molecular, metabolic, and electrophysiological studies to identify fingerprints for the early detection for psychiatric disorders.
- Development of advanced data analysis tools to further decode and understand the information flow in the living human brain from multimodal recordings.
- Knowledge transfer on advance imaging methodologies such as combined PET-MRI-EEG and Ultra-High Filed (UHF) MRI combined with PET, MEG, EEG, , to better suit research questions about psychiatric disorders.

Steps to create career for alumni:

The success of this cluster proposal will hinge on interdisciplinary support from our key personnel, the recruitment and training of qualified junior researchers, and inter-cultural competences. This can be guaranteed by the successful completion of ongoing research in the different roadmaps (RM1 – RM4). To ensure the sustainability of this cluster, we will train junior research to accomplish research independence under the umbrella of this cluster and their corresponding institutions upon arrival in Palestine. To achieve this, the following things need to be considered:

1. Students who are currently completing their postgraduate studies at Jülich will join and extend the research cluster.

2. Extend existing collaborations: by aggregating Palestinian and German researchers who are experts in the field of neuroscience, neuroimaging, molecular biology, and advanced data analysis.
3. Supervision of projects: allow new graduate students (MSc. & PhD) to complete their studies in Palestine in the research cluster.

Proposed Infrastructure

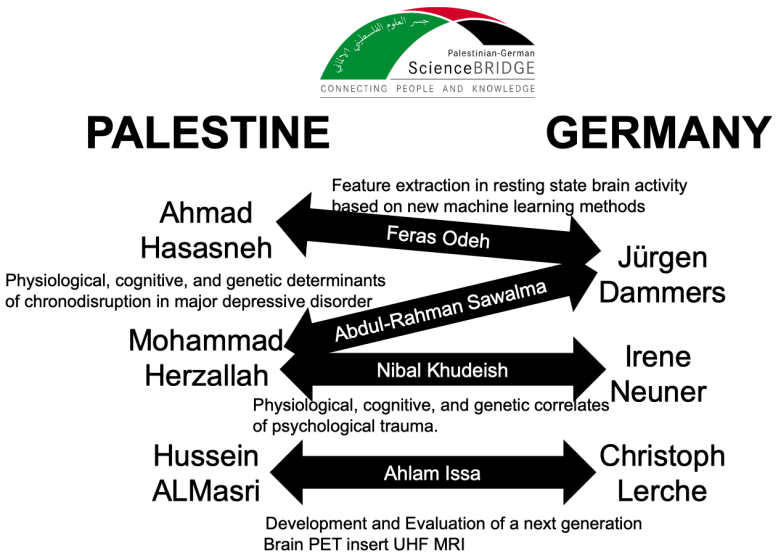
Successful implementation of the proposed research cluster will ensure sustainability in providing not only background and motivation for future studies in neuroscience, but also a platform for alumni researchers to lead independent research groups in Palestine.

Successful realization of the proposed cluster and its sustainability heavily depends on the support for the scientific exchange with all collaborating partners including the employment and exchange of qualified students, support for research expenses, and infrastructure and capacity building in both Palestine and Germany. All project partners agreed to continue the scientific collaboration by means of the establishment of follow-up projects in the fields of neuroscience and medical imaging in both sites. This will require:

- Financial support from the government for doing neuroscience research independently in both Palestine and Germany.
- Official commitments (such as scientific cooperation agreement, SCA; material transfer agreement, MTA; …etc.) from FZJ, German and Palestinian Universities and PALAST are needed to cover current and future activities.
- For each existing roadmap in this cluster a seed of one postdoctoral researcher (alumnus) is required (4 in total) to work between Palestine and Germany to ensure the sustainability of the collaborations, research activities, on-site trainings, and the establishment of research niches for our alumni.
- INM-4 (FZJ Germany), PAU (Palestine), AQU (Palestine) and the PNI/AQU (Palestine) will provide access to the research infrastructure, training and data needed to complete the proposed projects
- State of the art research equipment in Palestine is required (modern EEG, High Performance Computer, various types instrumentation for simulations and real experiments) to carry out the proposed studies in parallel and build infrastructure in Palestine.

Prospective

The research cluster will integrate the principal investigators' expertise at various universities and research institutes in Palestine (AQU/PNI, PAU), and Germany (RWTH Aachen, FZJ/INM-4). Successful completion of our studies can significantly advance our understanding of key factors that, for example, regulate the expression of major depressive disorder (MDD) symptoms. MDD is one of the leading causes of disability and death worldwide. Palestine is on the top of the list of West Asian countries with the highest prevalence of MDD. This mental health epidemic represents one of the major struggles for the healthcare sector in Palestine. Our studies will present a cross-cultural account that link biology to cognition, and ultimately mental health.
Bringing together the expertise of both partners in this consortium will ensure the development and applications of novel imaging and data analysis methodologies that are expected to have significant impact on future brain research.



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Research interest of Jülich and Palestine

Summary of ongoing research as defined by roadmaps (RM)

RM1: Neural Correlates of Depression and Chronodisruption

PIs: Jürgen Dammers (INM-4/FZJ), Mohammad M. Herzallah (PNI/AQU); PhD student: Abdul-Rahman S. Sawalma

Circadian rhythms regulate a myriad of physiological functions following various environmental cues, especially light (zeitgeber). They constitute a 24-hour cycle with variable start and end points that are referred to as "chronotypes". Disruption of circadian rhythms contribute to the pathophysiology of various psychiatric disorders. For instance, in major depressive disorder (MDD), patients exhibit a generalized disruption of their circadian rhythm in the form of disturbances in sleep, hormonal, mood and temperature rhythms. Only little is known about the influence of distorted circadian rhythms, which not only interfere with the individual working productivity in adults or the learning ability in children, but is also discussed to have a psycho-somatic or psycho-social effect. The sensitive interplay of the internal temporal order of physiological, biochemical and behavioral rhythms can be distorted leading to chronodisruption. This has been closely associated with an increased risk of developing certain disorders, such as MDD. Cognitive reports suggest that MDD is associated with a selective deficit in learning from positive feedback, thus echoing the symptoms of loss of pleasure. To date, very little effort has been invested to understand the spatio-temporal organization of the neural signal that underlies circadian rhythm variations in MDD.

In this project, we will explore the electrophysiology of MDD and chronodisruption using magneto- and electroencephalography (MEG/EEG). We will examine the neural pathways involved in reinforcement learning. The objective of this project is to:

(1) Determine the association of chronodisruption with various symptoms of MDD in the Palestinian and German population while examining cultural factors as covariates.
(2) Investigate chronotype as a potential mediator of response to antidepressants in our future studies on MDD.

In this proposal, we will combine and strengthen expertise in both sites. Thus, the present study will further contribute to the question whether there is evidence for a dependency of chronotype on the expression of MDD symptoms. We will investigate the information flow by means of connectivity and

causality analysis to extract neuro-oscillatory signatures of cognitive or task-performance based brain activations at very high temporal resolution using MEG (FZJ) and EEG (AQU).

The current research proposal facilitates, for the first time, a comprehensive and multicultural view of chronotype-specificity, including its associations to well-being and MDD. The project aims at exploring the underlying spatio-temporal organization of the circadian neural networks in MDD and healthy states.

RM2: The Cognitive Correlates of Genetic and Epigenetic Variations in the Dopamine System in Psychological Trauma

PIs: Irene Neuner (Aachen University, INM-4/FZJ), Mohammad M. Herzallah (PNI/AQU); PhD student: Nibal Khudeish

Exposure to psychological trauma, and potential development of post-traumatic stress disorder (PTSD), has been linked to alterations in feedback-based learning. However, sensitivity to positive and negative feedback varies considerably among individuals as a function of synaptic dopamine availability. Converging evidence suggests that naturally-occurring polymorphisms in the dopamine transporter gene (DAT1) affect the concentration of synaptic dopamine by regulating the expression of the dopamine transporter. Further, the DAT1 has an abundance of methylation sites that makes it an ideal target for epigenetic changes.

In this proposal, we will explore the cognitive correlates of genetic and epigenetic variations in the dopamine system in the context of psychological trauma exposure. In our studies, we will test: (1) Healthy subjects without trauma exposure, (2) Trauma-exposed healthy subjects, and (2) Patients with PTSD. These studies will integrate the principal investigators' expertise at the Palestinian Neuroscience Initiative (PNI), Al-Quds University, Palestine, and the INM4 at the Forschungszentrum Jülich, Germany. We will utilize approaches in cognitive neuroscience, neurogenetics, epigenetics, neuro-psychiatry, computational neuroscience, and machine learning. In particular, we aim to accomplish the following specific aims:

AIM-1 Study the cognitive effects of naturally-occurring genetic polymorphisms in DAT1 in the context of psychological trauma. We will examine two variable-number of tandem repeats polymorphisms in the 3' untranslated region (3'-UTR VNTR) and in intron 8 (Int8 VNTR) were shown to regulate dopamine transporter activity. A higher number of repeats in the 3'-UTR VNTR polymorphism, but a lower number of repeats in the Int8 VNTR polymorphism, were associated with higher activity of the dopamine transporter, and subsequently, lower synaptic dopamine, and vice versa. We use a computer-based cognitive task that dissociates positive and negative feedback learning to evaluate healthy subjects, trauma-exposed healthy subjects, and patients with PTSD.

AIM-2 Investigate the epigenetic and cognitive changes in the DAT1 gene as a consequence of psychological trauma. Using a pool of healthy subjects that were tested at the PNI since 2009, we will recruit healthy subjects who were exposed to psychological trauma after the initial testing. We will examine the DAT1before and after psychological trauma exposure for methylation changes. We will also evaluate trauma-exposed healthy subjects before the initial testing, and healthy subjects without any trauma exposure.

AIM-3 Examine resting-state connectivity, event-related potentials, and oscillatory power as a function of psychological trauma exposure. We will use electroencephalography (EEG) examine the physiological markers for DAT1 variations in the context of psychological trauma. We will focus on cortical regions that were linked to PTSD symptoms such as the dorsolateral prefrontal cortex and the anterior cingulate cortex. We will cross-sectionally evaluate healthy subjects, trauma-exposed healthy subjects, and patients with PTSD.

At the PNI, we will focus on the genetic, cognitive, and EEG experiments on both healthy subjects trauma-exposed healthy subjects, and patients with PTSD. At the INM4, we will conduct the MEG experiments, NIRS-EEG and 7T MR imaging on healthy subjects. We will integrate the data analysis across the PNI and INM4 sites to unify the approaches. The double affiliation of Irene Neuner, University Hospital RWTH Aachen, Acting Chair of Psychiatry and Forschungszentrum Juelich will offer access to psychiatric patient cohorts.

Successful completion of our studies can significantly advance our understanding of the cognitive and genetic basis of psychological trauma. Given the worldwide attention to PTSD, and the high prevalence in Palestine, our studies present an ample opportunity to understand the biological underpinnings of a psychological construct. Dopamine has been implicated in a myriad of neuropsychiatric disorders. Understanding its role in the consolidation of psychological trauma, and potential conversion to PTSD, can move us a step closer toward developing patient-centric treatments that traverse the genetic, cognitive, and symptom domains.

RM3: Highly quantitative PET/MR imaging for psychiatric disorders

PIs: Christoph Lerche (INM-4/FZJ), Hussein AlMasri (AQU), PhD student: Ahlam Issa

MRI allows for high spatial resolution structural imaging with high soft tissue contrast, a series of functional mappings, such as perfusion weighted imaging (PWI), diffusion weighted imaging (DWI), and proton magnetic resonance spectroscopy (^{1}H-MRS). In particular, functional MRI (fMRI) allows visualizing the brain activity via measurement of the blood oxygenation level dependent (BOLD) effect. Compared to MRI, PET has a million-fold higher detection sensitivity and is, therefore, the most important, non-invasive, molecular imaging modality in humans, especially in neuroscience. Moreover, dynamic PET together with fast blood and plasma analyses and subsequent kinetic modelling allows collecting highly quantitative data of physiologically relevant parameters and metabolically active substances. Since the late seventies, functional PET studies have contributed significantly to the understanding of cerebrovascular diseases, dementia, movement disorders, epilepsy, schizophrenia, addictive disorders, depression, anxiety disorders, brain tumors and last but not least to understanding the healthy brain [1].

The combination of PET and MRI techniques enables a unique access to both function and structure of the human brain and thus provide an objective biomarker for psychiatric disorders, where, due to the absence of imaging biomarkers, the routinely diagnosis still must be based on description and classification of behaviors [2]. Hybrid PET/MR promises this simultaneous measurement of phenotypic variations in those brain circuits, which are expected to be associated to the observed alterations in behavior. Of special interest in this context is the ability of PET to measure neuroreceptor densities and also changes in their occupancy induced either by exogenous occupancy studies (pharmacological challenges) or endogenous release and competition [3]. However, quantitation precision and accuracy of state-of-the art PET imaging devices currently limit the observation to endogenous effects with effect sizes of least 10-20%. The reasons for this are manifold. Besides the intrasubject and test-retest variabilities of the objects, especially the limitations of the PET technology are responsible for this high threshold, in particular high statistical noise in PET images, approximations in the scatter correction algorithm [4], deficiencies of currently existing motion correction methods [5], different data correction methods as dead time correction and random correction, and quantitation biases caused by iterative image reconstruction algorithms at low activity concentrations [6].

The INM-4 is currently developing and building a new-generation UHF-MRI compatible Brain-PET-insert for dedicated neuroimaging. The Brain-PET-7T is planned to be operated in UHF-MRI scanners and is expected to offer a 3 to 4-fold increase in sensitivity and a markedly improved and more homogeneous spatial image resolution of 1.5-2.5 mm over its FOV. The mere increase of sensitivity and spatial resolution of this newly build device will considerably lower the threshold for detectable endogenous neurochemical changes. A further reduction of this threshold should be achieved by improving the mentioned data correction algorithms, mainly motion correction approaches and scatter correction with less approximations. These activities are in-line with the focus of a current project within the PGSB framework, which aims at improving the dead time correction for dedicated brain PET scanner. Within this cluster activity, we aim at reaching a quantitation accuracy of 1% for the newly build PET insert. Moreover, many aspects of methodological development and system development for PET and combined PET/MR imaging can be addressed via Monte Carlo simulations, where experimental verification can be done at the institutes with the corresponding instrumentation. This enables an ideal scenario for a distributed development within the proposed cluster.

References

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RM4: Deep learning-based predictions from neuroimaging data in patients with psychiatric disorders

PIs: Jürgen Dammers (INM-4/FZJ) and Ahmad Hasasneh (PAU), Phd student: Feras Odeh

Brain imaging modalities operate at different spatial and temporal scales, thus providing various measures of biophysical quantities at different resolution and signal-to-noise ratios (SNR). These multivariate datasets offer a great possibility to uncover the spatio-temporal dynamics of the living human brain, however, data analysis remains challenging. Not only the spatial and temporal resolution of the acquired information differ across modalities, but also the nature of the data, where each modality measures one component of the same biological process. Typically, data analysis is applied separately for each data set, thus ignoring the comprehensive information content of the in synchrony recorded data. Recent endeavor from various neuroimaging groups record that neuroscientists claim that there is a need in combining and extracting all available information from the multivariate data sets in order to better understand the spatio-temporal dynamics underlying specific brain function. In our recent study, we introduced a combined deep convolutional neural network for the classification of ocular and cardiac activity in magnetoencephalographic (MEG) data [1]. In this study it has been shown that the combination of two different neural network strategies, i.e., deep learning network (DNN) and convolutional neural network (CNN), were able to identify complex structures in complex high-dimensional data and outperformed each single network design (Figure 1).

In this project, we will combine different strategies from deep learning techniques to automatically extract biological fingerprints from functional neuroimaging data. To understand the complexity of neural networks while the brain is in action it is mandatory to extract and investigate the so-called feature maps in space, time and frequency domains. Featuring a late fusion technique, the cross- or multimodal feature extraction is optimal for combining functional magnetic resonance imaging (fMRI), with electroencephalography (EEG) and cross-modal data analysis using fMRI and MEG data. We think that deep learning-based approaches will play an important role in bridging different scales from different imaging modalities with a potential to provide a diagnostic tool [2]. Deep learning-based approaches, such as CNN and DNN, have outperformed the existing machine learning methods in several neuroimaging applications including prediction and diagnostic [3].

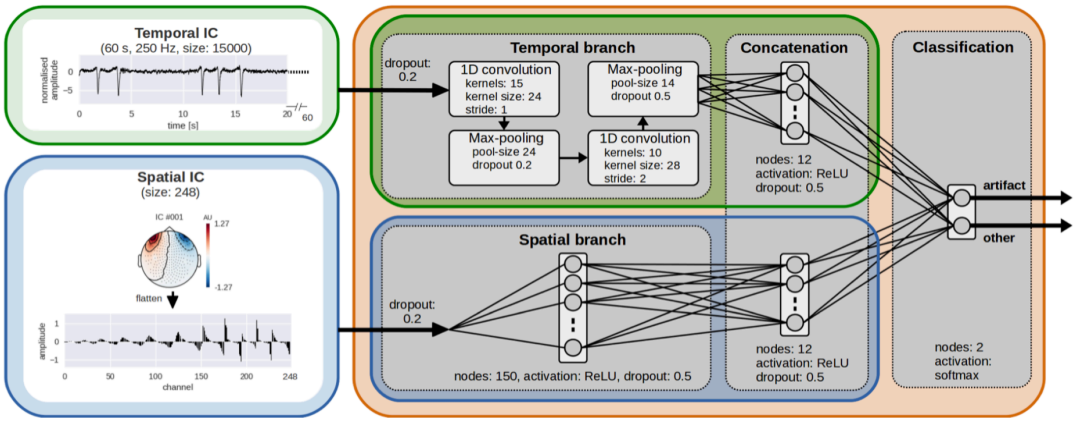

Figure 1: Combined deep and convolutional neural network for the analysis of spatio-temporal features in neuroimaging data (results were published in [2]).

References

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