

ERA-Net Neuron

NEWSLETTER 18



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New!!! You can subscribe to our newsletters at

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The ERA-NET NEURON has launched its new Joint Transnational Call on "Mental Disorders" on January-10, 2013.

ERA NET NEURON opened its new Facebook page

Become our friend and get updates on our activities in supporting multinational research on neurological diseases and keep in touch with other NEURON Facebook friends.

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More information can be found in our web page
<http://www.neuron-eranet.eu/index.php>



Final Scientific Symposium on Development and Advancement in Methods and Technologies Towards the Understanding of Brain Diseases January 2013, Dead Sea, Israel

In 2009, the ERA-Net NEURON launched a joint transnational call for proposals on novel methods and technologies in neuroscience. The scope of this call was method development – ranging from optical, genetical and/or electrophysiological to modeling approaches, or combinations thereof - beyond specifically defined diseases. For projects along the "Development and advancement in methods and technologies towards the understanding of brain diseases" only interdisciplinarity and the involvement of 3-5 groups from minimum three different countries were requirements to be met. The research question, technique(s) and methodologies were to be liberately chosen according to the necessities of the addressed problem.

At an ERA-Net NEURON symposium held at the Dead Sea, in January 2013 the ten since February 2010 funded projects presented their results. The symposium demonstrated threefold success, as Dr. Marlies Dorlöchter, the coordinator of the ERA-Net NEURON, summarized:

- First, for the funding organizations within the ERA-Net NEURON. Their representatives highly acknowledged the reward of the funding investments, visible – among other criteria – by a more than reasonable number of outstanding results.

- Second, the researchers themselves. Prof. Rafael Fernández-Chacón appraised the unbureaucratic funding procedures that promoted early-on creative project work and the possibility for intergroup-networking.
- Third and not least, neuroscience because the many methodological and technological developments impact on the understanding of brain functions in normal and disease conditions – cutting edge research!



The symposium was rounded up by a poster tour

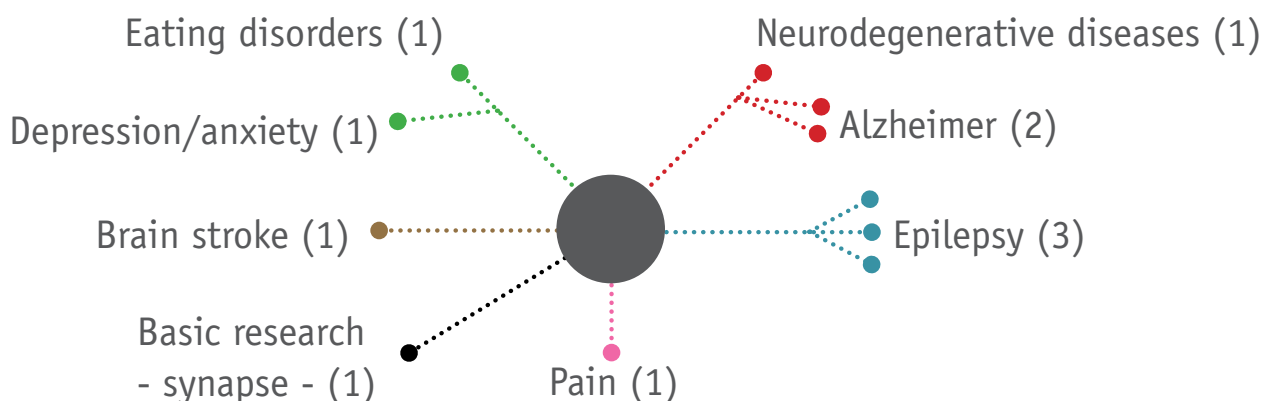
The symposium was opened by Dr. Benny Leshem of the Chief-Scientist-Office of the Ministry of Health (Israel) that kindly hosted the meeting. He summed up the 2009 intentions of funding organization when the call was launched. Research projects had to be hypothesis-driven and combine cutting-edge technologies with a clear, neuroscience related research question.

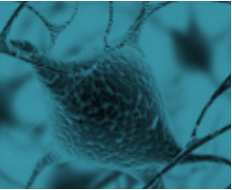
The challenges for understanding how the brain (dys)functions at multiple levels of integration are numerous. Thus, recent technical developments open promising new avenues for a better understanding of the functional mechanisms in the brain. In inspiring contributions all speakers, Sumi Leung, Antoni Valero-Cabre, Arthur Konnerth, Vania Broccoli, Jochen Herms, Carsten Korth, Claus Pietrzik, Rafael Fernández-Chacón, Bernard Bioulac and Heinz Beck presented their results, outcomes and potential new research questions (please visit also www.neuron-eranet.org). The symposium provided an excellent view on the technological progresses in the field of disease-related neurosciences. In concluding remarks all researchers mentioned that they would be keen to collaborate again, should the opportunity arise, because "...the ERA-Net NEURON funding gave much more freedom to do good science compared to other funding measures".

ERA-NET NEURON fifth Joint Transnational Call

Novel Methods and Approaches towards the Understanding of Brain Diseases

Following the success of the Joint Transnational Call (JTC) in 2009 on novel methods in Neuroscience, ERA-NET NEURON launched a another Call on the same topic in January 2012, which elicited a stunningly robust response from applicants. Therefore, Neuron's fifth JTC for multi-national collaborative research focused on novel methods and approaches towards the understanding of brain diseases. Most proposals responding to the JTC were multidisciplinary in nature, covering a broad spectrum of theoretical and technical aspects of neurosciences, including: imaging technologies ; pharmacology; molecular, (epi)genetic and "omics" approaches; stem cells and neural differentiation in relation to cell therapy; gene targeting to the brain; molecular modeling, electrical and magnetic brain stimulation, and behavioral and epidemiological methodologies. Altogether, 184 eligible research consortia comprising 736 research groups from 14 countries submitted their proposals. Of these, 11 applications were approved for funding totaling € 11 million. The winning proposals are described briefly on the pages that follow.





ABETA ID \ \ PREPARATION OF AMYLOID-BETA AGGREGATE SPECIES FROM SYNTHETIC AND PATIENT-DERIVED MATERIAL TO DEFINE DISEASE-CAUSING MECHANISMS

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

PROJECTS RECOMMENDED FOR FUNDING

Alzheimer's disease belongs to the neurodegenerative diseases, which cause nerve cells in the brain to degenerate and die. This process believed to be caused by proteins that fold abnormally and therefore cannot function correctly. In post-mortem brain of Alzheimer patients, researchers have found several abnormal structures formed from the amyloid-beta protein but could not yet determine which are responsible for disease. Is it large fibrils that disturb the neuronal metabolism or rather smaller oligomeric structures? Current evidence indicates that small oligomers disturb the neuronal metabolism. In order to study these oligomers in detail, it is necessary to have sufficient amounts. This proves difficult, as they are present in post-mortem brain only in very small quantities. This project therefore sets out to establish a method with which oligomers derived from biological samples can be used as templates that cause readily available synthetic protein to form oligomers as well. With this amplification method we aim to provide a valuable tool for the successful elucidation of the process of protein misfolding and aggregation in Alzheimer's disease and how it leads to neurodegeneration. Also, we will use template mediated oligomers to find new chemical or biological entities with therapeutic potential for this devastating disease.

PROJECT PARTNERS:



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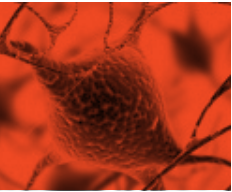
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CIPRESS \ \ CELL STRESS INDUCIBLE PROTEIN EXPRESSION SYSTEM FOR RECOVERY FROM SEIZURES PROJECT DESCRIPTION:

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

The epilepsies are chronic neurological syndromes that severely degrade life quality, due to the unpredictable occurrence of seizures. Most temporal lobe epilepsy (TLE) syndromes have no discernable genetic component, suggesting that epileptogenesis depends on disease-promoting mechanisms of neuronal plasticity. The pathological changes underlying TLE are induced by multiple brain insults, such as traumatic injury, infection, stroke, intracerebral hemorrhage and infantile convulsions. Yet, brain mechanisms involved in this process of epileptogenesis are only partially understood. Neuronal death and glial activation is often an early component. Subsequent changes may affect neuronal pH and Cl⁻ regulation, energy metabolism, and inhibitory actions of the neurotransmitter GABA. Thus, this proposal aims to develop novel approaches to identify the molecular mechanisms underlying not only disease-promoting but also adaptive mechanisms triggered during epileptogenesis. This information will let us test specific strategies to block processes of epileptogenesis. We will use a novel molecular tool (CIPRESS) which permits induction of protein expression in response to cellular stress during epileptogenesis. We will ask which candidate proteins (or combinations) can suppress seizure activity in animal models of epilepsy as well as in organotypic hippocampal slice cultures of human patients with TLE. This approach should both provide insights into molecular, cellular and network mechanisms of epileptogenesis and also permit rigorous tests for the development of a gene therapy based on the molecular processes involved.



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F4T \ \ FOODFORTHOUGHT: THE EPIGENOMICS OF EATING DISORDERS

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

Food gives us the energy and nutrients that we need to survive. However, overeating in today's society can lead to unwanted, debilitating effects on our health. It is now becoming clear that our genes have an important role in controlling how we respond to starvation and overeating. Foods high in fat, salt and sugar, for example, manipulate our brain in a way similar to drugs of abuse, and may thus be addictive.

Since genes have different roles in different parts of our brain, we need to understand how those genes exactly function in the different brain regions and within the specialized cell types. Toward this goal, five European groups have teamed up to study how our genetic makeup responds to starvation, compulsive overeating and habitual food-seeking. We delve deep into the brain of two model organisms, which share all fundamental mechanisms involved in feeding and behavior with humans. Using latest generation DNA sequencing methods and computational modeling, our joint project seeks to provide a list of genes within specialized brain regions likely to contribute to eating disorders. With this detailed insight into how our genes shape our interaction with food, we will have a more systematic, genome-wide insight to further our understanding of how obesity and addictive behaviors develop. In the long term, our novel approach is a timely opportunity to work toward novel drugs that could improve the lives of millions.

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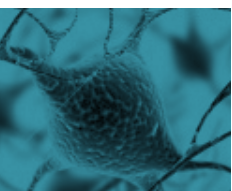
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LIGHTPAIN \ \ DECIPHERING THE ROLE OF PERIPHERAL AND CENTRAL NERVOUS SYSTEM METABOTROPIC GLUTAMATE RECEPTORS IN NEUROPHATIC PAIN WITH PHOTOACTIVABLE LIGANDS

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

PROJECTS RECOMMENDED FOR FUNDING

Pain is one of the main medical problems that quite often results into a chronic disease with limited effective treatment. Pain transmission is a complex process involving nerves, the dorsal horn and the brain in a fast and effective communication. The way whereby pain is transmitted from local injury to the brain is complex and only partially known. It involves high precision biological machinery with a number of processes and elements working in a coordinated fashion. The limited knowledge of this mechanism hampers the development of better drugs and treatments for pain.

The LIGHTPAIN project is aimed to the control of drug activity by molecules that can be switched on by light, and their use to understand the role of metabotropic glutamate (mGlu) receptors in pain transmission. The objective is to develop subtype-selective mGlu receptor ligands (positive or negative allosteric modulators) that are photochemically triggered and can therefore interact with mGlu receptors only at sites (peripheral or central) that are spatiotemporally exposed to light. These light-controlled molecules and the techniques for optical ligand delivery to the spinal cord, brain and peripheral nerves will be used to understand how mGlu receptors critically regulate pain threshold under pathological conditions.

The acquired knowledge will help to better understand the mechanism involved in pain and to establish a pharmacological technique based in the local light activation of receptors that can be applied to other drug targets.



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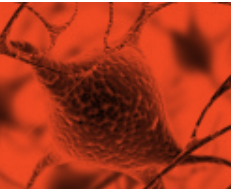


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MICRODEG \ Neuronal Networks in microfluidic chips for the study of propagative neuronal disorders

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

Neurological syndromes such as Alzheimer, Parkinson and Huntington diseases shares similar degenerative signatures by promoting progressive aggregation of endogenous proteins in the brain. Recent evidences have shown that similarly to infectious prion diseases, pathological hallmarks of these syndromes spread progressively along neuronal pathways in the brain. The reason underlying these processes are unknown. They could involve several non exclusive phenomena ranging from abnormal synaptic transmission, progressive disconnection of neuronal hubs; to the spreading of aggregated proteins in between neurons. While these processes are classically studied in whole animals, reliable in vitro model that allows the precise and fast study of molecular and cellular responses in an ordered environment are lacking. Using cutting edge technologies we propose to develop micro-brain platforms allowing the in vitro reconstruction and manipulation of both rodent and human neuronal networks. These new experimental systems will be used to study the underlying mechanisms involved in the spatial progression of neurodegenerative hallmarks of Parkinson and Huntington diseases and test whether scenario proposed in mouse models (prion-like propagation) are pertinent for human. Overall in addition to the testing of a fundamental biology question, the proposed project goes with the trend of building “organ on chips” that are envisioned to allows production accurate models for the study of human diseases.



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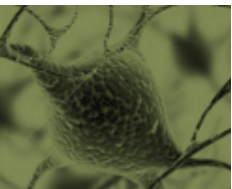
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nEUAPPs \\ CNS delivery of the secreted amyloid precursor protein ectodomain APPs: Effects on brain physiology and therapeutic potential for Alzheimer's disease

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain


PROJECTS RECOMMENDED FOR FUNDING


Alzheimer's disease (AD) is the most common cause of age-related dementia affecting about 5% of adults above 65 years with a doubling prevalence every 5 years. In view of an aging society and with respect to economic and social impacts the need for effective therapies becomes obvious. Although described already in 1906, up to now molecular causes of AD are not fully understood. Post mortem brains of AD patients contain so called neuritic plaques which are extracellular deposits composed of a short peptide, the β -amyloid. This peptide is cleaved from the widely expressed amyloid precursor protein (APP). Despite the central role of APP for AD pathogenesis the physiological role of APP and the related APP like proteins is still poorly understood. However, increasing evidence indicates that a loss of signals mediated by APP family proteins may contribute to AD pathogenesis. Within this collaborative project we therefore aim at further elucidating the role of APP family proteins and their fragments for brain physiology and to assess how we can exploit these functions for AD therapy. These studies will involve the analysis of genetically engineered mouse mutants in comparison to non-treated controls with respect to brain physiology, neuronal, morphological, behavioral, and cognitive improvements.

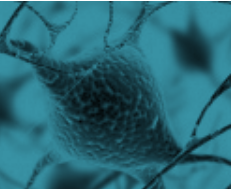
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RENEW IT \\ Restoring function in stroke via GPR17, a new receptor involved in adult brain self-repair

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PROJECTS RECOMMENDED FOR FUNDING

Loss of oligodendrocytes, the myelin-forming cells ensheathing axons and ensuring nerve transmission, is not only typical of demyelinating diseases but also markedly contributes to stroke deficits. Remyelination thus represents a new attractive approach to foster functional recovery over a wider therapeutic window in stroke patients.

In mice models of brain ischemia, RENEW IT will exploit the complementary expertise of participating Partners to expand the population of oligodendrocyte precursor cells in the rodent brain and then instruct generated cells to differentiate to myelinating cells by using new pharmacological agents acting on a recently discovered oligodendroglial actor, the GPR17 receptor.


The efficiency of this approach will be monitored in living ischemic animals by non-invasive imaging techniques allowing the detection of myelin restoration after stroke; in parallel, behavioural measures will be performed in alert animals to determine whether and to what extent higher integrated brain functions, such as learning and memory, are positively influenced by these treatments.

RENEW IT will provide new information on the extent and modalities of brain self-repair through white matter reconstruction and help developing new strategies to stimulate remodelling of neuronal circuitries after stroke.



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SEMAINE \\ SIMULTANEOUS MEG OR FMRI AND INTRACRANIAL EEG

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

The basis of brain function and communication between neurons is the production of electrical activity that translates into brainwaves when recorded with electroencephalography (EEG) or magnetoencephalography (MEG). High-frequency brainwaves are known to represent a major component of normal brain processing, but sometimes also appear abnormally in association with epilepsy. They are often too weak to be easily detected from external measurements like scalp-recorded EEG or MEG. In fact, such brainwaves are usually captured by using intracerebral electrodes (icEEG) in patients with drug-resistant epilepsy. Thus, using icEEG, one can record both abnormal high frequency brainwaves that help locate the epileptic focus, and normal high frequency activity which allows assessing the functional role of the epileptic brain regions that might be resected in order to avoid removing important cerebral tissue. However, due to the limited number of electrodes that can be placed in a patient's brain, information regarding normal and abnormal high frequency brainwaves remains suboptimal.

Our research project aims to address this important limitation by performing icEEG recording of high frequency brainwaves with simultaneous MEG and functional magnetic resonance imaging (fMRI). The two latter imaging methods can explore the function of the entire brain noninvasively, and if coupled with icEEG, provide information regarding changes occurring in virtually every brain region when local high-frequency brainwaves are detected by intracerebral electrodes. Ultimately, this will allow us to develop new methods to accurately infer the location and extent of high-frequency activity within the brain purely from noninvasive imagery.

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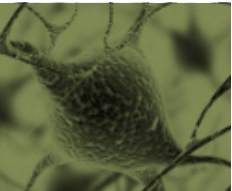
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TargetECM \ \ SUPERRESOLUTION IMAGING AND THERAPEUTIC TARGETING OF EXTRACELLULAR MATRIX-MEDIATED SIGNALLING IN BRAIN DISEASES

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

Many brain diseases are due to a failure in communication between neural cells, which takes place in highly specialized intercellular contacts, synapses. Among these are depression, addiction, mental retardation, autism, anxiety, schizophrenia, migraine, stroke, epilepsy, chronic pain, Alzheimer's and Parkinson disease. The TargetECM project aims to investigate the role of the least studied component of synapses, the extracellular matrix, in epilepsy and Alzheimer's disease. The extracellular matrix is a complex structure composed of molecules secreted from neurons and glial cells, which accumulate at the extracellular space and control various aspects of synaptic communication. In the frame of TargetECM project, four research groups from Germany, France and Israel will break new ground by investigating the (patho-)physiological functions of several prominent extracellular matrix molecules, such as LGI1 (leucine-rich, glioma-inactivated 1), heparan sulfate proteoglycans and integrins. By developing new imaging probes and combining their expertise in extracellular matrix functions, protein engineering and advanced imaging, these groups will improve our understanding of the basic mechanisms of communication between neural cells that are at fault during patho-physiological alterations, thereby identifying new therapeutic targets for treatment of neurological and neuropsychiatric disorders.



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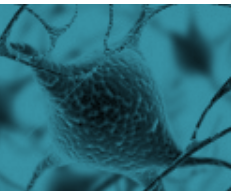
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TBI Epilepsy \\ Proteolytic remodeling of the extracellular matrix in aberrant synaptic plasticity underlying epilepsy evoked by traumatic brain injury

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

PROJECTS RECOMMENDED FOR FUNDING

Traumatic brain injury (TBI) is major health problem. Yearly cost from TBI in Europe exceeds €100 billion and is steeply rising. There are no therapies to improve the recovery or to prevent the development of life-compromising comorbidities. One of the major long-lasting consequences of TBI is post-traumatic epilepsy (PTE). However, almost nothing is known about the mechanisms that lead to the development of epilepsy (epileptogenesis) after TBI. Recent evidence shows that the extracellular matrix (ECM), which surrounds neurons and glia, plays a major role in remodeling of neuronal connections after injury. In particular, the two enzyme systems – matrix metalloproteinase-9 (MMP) and urokinase-type plasminogen activating system (uPA) – can degrade various components of the ECM, enabling the occurrence of very focal and targeted plastic changes. We plan to test a hypothesis is that MMP-9 and uPA systems play a major role in reshaping the brain connections during development of epilepsy after TBI. We will investigate whether animals with genetically modified MMP-9 or uPA systems have altered susceptibility for post-TBI epileptogenesis. In parallel, we will investigate whether patients who have suffered TBI have mutations in MMP-9 or uPA systems, and whether the levels of these molecules are changed at acute post-injury phase. We will also investigate when, and in which brain areas, MMP-9 and uPA systems are active after TBI, and what are the molecular mechanisms that mediate their effects. The major goal of our research is to reveal novel mechanisms that can be used as treatment targets to be developed to prevent post-traumatic epilepsy.



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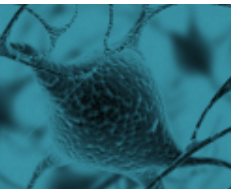
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WN2NA \ \ WHITE MATTER IMAGING, MICROSTRUCTURE, AND NEGATIVE AFFECTS: TRANSLATIONAL STUDY IN HUMANS AND MICE

Austria \ Belgium \ Canada \ Finland \ France \ Germany \ Israel \ Italy \ Luxembourg \ Poland \ Portugal \ Romania \ Spain

Mood and anxiety disorders affect more than 100 million of Europeans and are still rising. The identification of noninvasive imaging biomarkers might inform on their early stages and course effects on brain structure. The affective disorders have been related to deviations of brain white matter connectivity as evidenced by diffusion tensor imaging (DTI). White matter imaging in depression could reflect myelin abnormalities. However, it is not clear what the changes seen through DTI refer to at the tissue and molecular levels.

This greatly limits the potential value of monitoring white matter alterations with DTI as a clinical tool. To which extent DTI alterations reflect changes in white matter maturation at adolescence and what are the molecular factors related with these changes cannot be tested in humans by non-invasive techniques.

The WM2NA project proposes to conduct cross-species DTI imaging studies (young participants and mice) to identify white matter changes that correlate with anxiety and depression symptoms. These changes could serve as translational and clinical biomarkers with clinical value. Novel insight on the molecular causes and consequences of altered white matter will bridge the gap from imaging findings to their cellular and molecular roots, thus opening new avenues for the understanding and prevention of major depression or related symptoms.

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