neuron
Network of European Funding for Neuroscience Research

Scientific Workshop "Neurodegeneration"

~ State of the art and future orientations ~

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SIXTH FRAMEWORK PROGRAMME

Contents

The Workshop was introduced by a welcome word from Frédéric Dardel, Scientific Director for Life Science at CNRS and followed by a word from the NEURON Coordinator Dr. Marlies Dorlöchter in order to explain the ERANET Neuron Scheme and the scope of the Workshop.

This Workshop is part of Work Package 4
Thematic input for programme of the NEURON project,
Work Package Leaders are Inserm and CNRS.
Powerpoint presentations and videos of the speakers'
presentations are available upon request from the Work Package Leaders.

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Foreword

It is now widely acknowledged that research in neurosciences is a major scientific challenge for the XXIst century. Understanding how the brain works is certainly of general interest. In addition, neurosciences are important for the development of new technologies, including for better interfaces between humans and machines. But perhaps more importantly for the public, progress in neurosciences is also critical for improving the treatment of neurological or psychiatric diseases. About a third of the total burden of diseases in Europe is due to neurological or psychiatric conditions. Understanding the causes and mechanisms of these diseases will ultimately allow finding efficient strategies for their prevention or treatment. Such progress will very much depend on neuroscience research.

The objective of the ERA-NET Neuron is to improve collaboration between national agencies in charge of funding neuroscience research in Europe, in order to coordinate and optimize their practices. One aim of Neuron directly relevant for researchers is to organize common calls between the participants to the ERA-NET. The first step in this process is to identify topics for the call which will have an added value for the field at a European level. In order to do that, the consortium will organize workshops at which experts will summarize the current questions and recent advances in specific areas of neurosciences. These workshops will help the Scientific Advisory Board to make recommendations to Neuron. The Paris workshop, organized by Inserm and CNRS was the first of this series. It was devoted to neurodegenerative diseases and included remarkable presentations on various aspects of the field from basic to clinical research. The efficacy of this first workshop is underlined by the fact that it led the way to a common call which has already been launched.

Jean-Antoine Girault
Inserm

Neurodegeneration

Neurodegenerative diseases are conditions in which cells of the brain and/or spinal cord die. The brain and spinal cord are composed of glial cells and neurons that have different functions such as controlling movements, processing sensory information, and making decisions. Aside from a small number of neural stem cells that are still able to divide, neurons of the brain and spinal cord are not readily regenerated, so excessive damage can be devastating. Neurodegenerative diseases result from malfunctioning and ultimately death of neurons which over time will lead to neurodegeneration and clinical disabilities. They can be crudely divided into two groups according to their major symptoms, although these are not mutually exclusive:

- Conditions causing problems with movements, such as paralysis or ataxia.
- Conditions affecting primarily memory and "higher" brain functions leading to dementia.

Brain damage can result from stroke, heat stress, head and spinal cord trauma, infections and various other causes. Neurodegenerative disorders usually refer to conditions in which there is no obvious external cause for the progressive destruction of neurons. In some instances the aetiology is a simple Mendelian genetic disorder. Although each of these hereditary neurodegenerative diseases are relatively rare they provide models to understand and attempt to treat related apparently non genetic diseases.

Many times neuronal death begins long before the patient will ever experience any symptoms. It can be months or years before any effect is felt. Symptoms are noticed when lots of cells have died and certain parts of the brain have been weakened to the point that they can no longer function properly.

Regulation, or production of microglia by the immune system, in a process of neuroinflammation, is currently being rigorously studied for its role in neurodegenerative diseases.

The best known neurodegenerative diseases include Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Lewy body dementia, multiple system atrophy. A well characterized example of neurodegenerative disease of genetic origin is Huntington chorea. Prion diseases have a very peculiar infectious origin and include Creutzfeldt-Jakob disease and bovine spongiform encephalopathy. Another infection-related condition which includes neurodegeneration is HIV-associated dementia.

One common aspect of neurodegenerative diseases is the paucity of available treatments. At present there are very few useful therapies. Treatment with L-dopa can improve symptoms of Parkinson's disease, but its efficacies disappear with time and side effects usually occur. Deep brain stimulation is then a very useful complement or alternative. Efforts are being made to develop therapies for Alzheimer's disease that will stabilize cognitive function at the level existing at time of diagnosis and treatment, but the results are so far disappointing.

Research is highly invested in stem cell technology and stem cell treatments, as well as gene therapy as possible ways to replace dying cells, provide neurotrophic factors and/or replace mutated genes. Although these approaches are promising they still have to demonstrate their usefulness in patients and their development is fraught with difficulties. Attempts to identify bio-markers as part of an attempt to understand the progression of certain types of neurodegenerative disease are also very important. In theory, if relevant bio-markers were identified, people could be treated for such diseases prior to onset of symptoms, thus resulting in a significant extension of their normal functional lifespan. As yet, however, the identification of bio-markers is in its infancy and consequently diagnosis of neurodegenerative disease tends to occur after the majority of neural damage has already been suffered by the patient.

Speaker 1: Professor Ignacio Torres Alemán

Spain.

TITLE: *"Loss of IGF-I input as a common cause of neurodegeneration".*

The vertebrate IGF trophic system includes various trophic factors and related molecules (insulin, IGF-I, IGF-II, IGF-III, relaxin 1 and 3, relaxin like factor…), their tyrosine kinase receptors (IR, IGF-IR…) and various regulatory proteins (IGF binding proteins). The release of IGF-I by the liver into the circulation is tightly controlled by growth hormone (GH) which is synthesized and secreted by the anterior pituitary. IGF-I is known to play a trophic role on many peripheral organs (muscles, bone etc), but it is possible that the GH/IGF-I axis could also play a crucial role in the brain (endocrine IGF-I) since systemic IGF-I is able to cross the blood-brain-barrier. Indeed, studies using systemic injections of labelled IGF-I have shown that circulating IGF-I is able to get into the brain and that IGF-I receptors present at the blood-brain-barrier mediate this process.

The physiological significance of the endocrine origin of brain IGF-I can be shown during physical exercise since 1/ exercise stimulates uptake of serum IGF-I by the brain and 2/ IGF-I mediates at least part of the beneficial actions of exercise on the brain (neuroprotection, neurogenesis). This has been demonstrated in the PCD mice (transgenic mice that display degeneration of the Purkinje cells in the cerebellum). The time spent in a rotating rod for PCD mutant mice is much lesser than for normal mice because of their loss in motor coordination. However, if PCD mice are submitted to physical exercise prior to the rota-rod test, their performance increase to reach the level of normal mice and this effect is abolished by the administration of an anti-IGFI. In wild type mice, the neuroprotective role of IGF-I induced by exercise, as well as its role in neurogenesis, has been demonstrated.

Circulating IGF-I levels could therefore have an impact on various human neurological diseases and have been shown to be modified in Alzheimer disease, depression, amyotrophic lateral sclerosis, multiple sclerosis, and other neurological diseases.

In Alzheimer disease, the protein amyloid-beta (A-beta) accumulates in the brain. Because IGF-I is able to modify the blood-brain-barrier function it could have a crucial role in Alzheimer disease since circulating IGF-I can promote A-beta clearance from the brain into the blood. Additionally, it has been shown that the blockade of IGF-I traffic or lower serum IGF-I levels produce Alzheimer-like neuropathology in rodents. Blockade of IGF-IR at the choroid plexus elicits cognitive loss together with a progressive brain amyloidosis and a tauopathy, while low serum IGF-I levels are associated to a deficit in learning and LTP induction in the hippocampus. Also, in healthy aging human, the cognitive status is negatively correlated with serum IGF-I levels, and brain aging could be in part due to a physiological loss of IGF-I input.

In conclusion, these data underlie the crucial beneficial role of circulating IGF-I in aging and late-onset dementia associated with Alzheimer disease. Thus, a combined deficiency or resistance to IGF-I can underlie or contribute to neurodegenerative diseases. This is particularly relevant in age-associated illnesses, such as Alzheimer disease.

Speaker 2: Professor Shlomo Rotshenker

Israel.

TITLE: *"Microglia activation in neurodegeneration (injury and disease): signalling phagocytosis".*

Microglia are immune-related cells (macrophages) that reach the central nervous system early in embryogenesis. Microglia is involved in neurodegeneration, and this can be illustrated by the huge increase in microglia activation observed in patients suffering from Alzheimer's disease.

How can be microglia associated with neurodegeneration?

Neurons can undergo cell death that can be due for instance to injury or to neurotoxicity processes through the administration of extrinsic toxins and also because of glutamate which is generated in the brain itself. As a consequence, microglia is activated and produces neurotoxic factors that generate more and more neuronal cell death. This detrimental vicious circle can start not only in neuronal cells, but also directly in microglia if they are activated by inflammatory stimuli.
However, activated microglia also plays beneficial roles in innate immunity, neurogenesis and phagocytosis of apoptotic cells or tissue debris (like degenerated myelin).
The balance between detrimental and beneficial functions of microglia is very delicate and the mechanisms are poorly understood.

Focus on phagocytosis of degenerated myelin

Degenerating myelin inhibits axon regeneration. Thus increasing phagocytosis of degenerated myelin debris could be beneficial for the regeneration of axons, which should therefore reach their target cells. Removing myelin debris is also important in neurodegenerative diseases like multiple sclerosis. Phagocytosis is one of the characteristics of microglia cells that can internalize degenerated myelin debris.
In the peripheral nervous system, axons are surrounded by myelin and axotomy induces a number of cellular events that trigger degeneration of the distal axon. This phenomenon is called "Wallerian degeneration" (WD) and is characterized by myelin destruction followed by a proliferation of activated macrophages that, together with Schwann cells, phagocyte and degrade myelin debris, thus removing obstacles for the repair of damaged neurons. Macrophages and Schwann cells actively involved in myelin phagocytosis express a molecule called Galectin-3/Mac-2 which is a good marker of this activation phenomenon. Macrophages and Schwann cells activation and myelin phagocytosis and degradation are orchestrated in time.
In the central nervous system, after axotomy, the distal portion of the degenerating axon can be divided in two domains. The more proximal domain, which is located around the injury site, displays activated microglial cells that phagocyte myelin very efficiently. More distally to the site of injury, myelin also degenerates but is not phagocyted because of a partial activation of microglia, as shown by the absence of induction of Galectin-3/Mac-2 in these cells. This later phenomenon is called "CNS-WD". However, in other models (such as Experimental Allergic Encephalomyelitis (EAE), an experimental model for multiple sclerosis), discrete regions of demyelination appear and activated microglia cells that display increased expression of Galectin-3/Mac-2 are recruited in these regions and are therefore actively involved in myelin phagocytosis.
While the pattern of activation of Galectin-3/Mac-2 can varies across these different degeneration models in order to promote or not phagocytosis, the expression of the receptors involved in myelin phagocytosis (which are CR3/MAC-1 for "Complement Receptor 3" and SRAI/II for "Scavenger Receptor AI/II") are up-regulated in CNS-WD and also in EAE regardless of the occurrence of the phagocytosis phenomenon.
These data emphasize that the receptors involved in myelin phagocytosis (CR3/MAC-1 and SRAI/II) have to be in an active state to allow internalization of myelin debris, and Galectin-3/Mac-2 could be the signal that promotes this receptor activation. Indeed, in vitro studies have demonstrated that Galectin-3/Mac-2 is necessary to stabilize the complex KRas-GTP (active form) that is involved in the intracellular cascade associated to these receptors, in order to allow phagocytosis.

In conclusion, these data highlight the primary role of Galectin-3/Mac-2 in myelin phagocytosis. One can imagine that the same molecular processes could be required for the phagocytosis of other particles, like for example, for the amyloid-beta protein or several pathogens that are invading the central nervous system in other neurodegenerative diseases.

Alzheimer's disease and other dementia

Alzheimer's disease (AD) is a primary degenerative disease of the brain. Dementia in Alzheimer's disease is classified as a mental and behavioural disorder in ICD-10. It is characterized by progressive decline of cognitive functions such as memory, thinking, comprehension, calculation, language, learning capacity and judgement. Dementia is diagnosed when these declines are sufficient to impair personal activities of daily living. Alzheimer's disease shows insidious onset with slow deterioration. This disease needs to be clearly differentiated from age-related normal decline of cognitive functions. The normal decline is much less, much more gradual and leads to milder disabilities.

The onset of Alzheimer's disease is usually after 65 years of age, though earlier onset is not uncommon. As age advances, the incidence increases rapidly (it roughly doubles every 5 years). This has obvious implications for the total number of individuals living with this disorder as life expectancy increases in the population.

The incidence and prevalence of Alzheimer's disease have been studied extensively. The population samples are usually composed of people over 65 years of age, although some studies have included younger populations, especially in countries where the expected life span is shorter (for example, India). The wide range of prevalence figures (1–5%) is partly explained by the different age samples and diagnostic criteria. In the Global Burden of Disease (GBD) 2000, Alzheimer's and other dementias have an overall point prevalence of 0.6%. The prevalence among those above 60 years is about 5% for men and 6% for women. There is no evidence of any sex difference in incidence, but more women are encountered with Alzheimer's disease because of greater female longevity.
The GBD 2000 estimates the DALYs (Disability Adjusted Life Years: the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability) due to dementias as 0.84% and YLDs (Years Lived with Disability) as 2.0%. With the ageing of populations, especially in the industrialized regions, this percentage is likely to show a rapid increase in the next 20 years.
The cost of Alzheimer's disease to society is already massive and will continue to increase. The direct and total costs of this disorder in the United States have been estimated to be US$ 536 million and US$ 1.75 billion, respectively, for the year 2000.

The exact cause of Alzheimer's disease remains unknown, although a number of factors have been suggested. These include disturbances in the metabolism and regulation of amyloid precursor protein, plaque-related proteins, Tau proteins, zinc and aluminium.

Biochemical characteristics

Alzheimer's disease has been identified as a protein misfolding disease, or proteopathy, due to the accumulation of abnormally folded A-beta and Tau proteins in the brains of AD patients.
A-beta is a short peptide which is a proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Although amyloid-beta monomers are soluble and harmless, they undergo a dramatic conformational change at sufficiently high concentration to form A-beta sheet-rich tertiary structure that aggregates to form amyloid fibrils that deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy.
AD is also considered as a tauopathy due to abnormal aggregation of the Tau protein, a microtubule-associated protein expressed in neurons that normally acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule-associated proteins, Tau is normally regulated by phosphorylation; however, in AD patients, hyperphosphorylated Tau accumulates as paired helical filaments that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques.

Neuropathology

Both amyloid plaques and neurofibrillary tangles are clearly visible by microscopy in AD brains. At an anatomical level, AD is characterized by gross diffuse atrophy of the brain and loss of neurons, neuronal processes and synapses in the cerebral cortex and certain subcortical regions. This results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus.
Alzheimer's disease is also accompanied by changes in various neurotransmitter levels. Indeed, the levels of the neurotransmitter acetylcholine are reduced as well as the levels of the neurotransmitters serotonin, norepinephrine, and somatostatin which are also often decreased. On the contrary, glutamate levels are usually elevated.

Disease mechanism

Three major competing hypotheses exist to explain the cause of the disease. The oldest, on which most currently available drug therapies are based, is known as the "cholinergic hypothesis" and suggests that AD is due to reduced biosynthesis of the neurotransmitter acetylcholine. The medications that treat acetylcholine deficiency have served to only treat symptoms of the disease and have neither halted nor reversed it. It is now clear that although alterations of cholinergic neurons do play a role it is only minor component in the disease process.

More recent research includes hypotheses centred on the effects of the misfolded and aggregated proteins, A-beta and Tau. The two positions differ with one stating that the Tau protein abnormalities initiate the disease cascade, while the other states that A-beta deposits are the causative factor in the disease. The Tau hypothesis is supported by the long-standing observation that deposition of amyloid plaques do not correlate well with neuron loss; however, a majority of researchers support the alternative hypothesis that A-beta is the primary causative agent.

The amyloid hypothesis is initially compelling because the gene for the amyloid-beta precursor (APP) is located on chromosome 21, and patients with trisomy 21 who have an extra gene copy almost universally exhibit AD-like disorders by 40 years of age. The traditional formulation of the amyloid hypothesis points to the cytotoxicity of mature aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cells calcium ion homeostasis and thus inducing apoptosis. A more recent and widely supported hypothesis suggests that the cytotoxic species is an intermediate misfolded form of A-beta, neither a soluble monomer nor a mature aggregated polymer but an oligomeric species. Relevantly, much early development work on lead compounds has focused on the inhibition of fibrillization, but the toxic-oligomer theory would imply that prevention of oligomeric assembly is the more important process or that a better target lies upstream, for example in the inhibition of APP processing to amyloid beta.

It should be noted further that ApoE4, the major genetic risk factor for AD, leads to excess amyloid build-up in the brain before AD symptoms arise. Thus, A-beta deposition precedes clinical AD. Another strong support for the amyloid hypothesis, which looks at A-beta as the common initiating factor for Alzheimer's disease, is that transgenic mice solely expressing a mutant human APP gene develop first diffuse and then fibrillar amyloid plaques, associated with neuronal and microglial damage.

Genetics

Rare cases of Alzheimer's disease are caused by dominant genes that run in families. These cases often have an early age of onset (usually <60 years). Nearly 200 different mutations in the presenilin-1 or presenilin-2 genes have been documented in over 500 families. Presenilins are involved in APP processing. Mutations of presenilin 1 (PS1) lead to the most aggressive form of familial Alzheimer's disease. Over 20 different mutations in the APP gene on chromosome 21 can also cause early onset disease. APP was the first AD gene to be discovered in 1987. These observations provide a strong support to the amyloid hypothesis discussed above.

There is currently no specific cure for Alzheimer's disease. Currently available medications offer relatively small symptomatic benefit for some patients, especially improving memory, but do not slow disease progression. The American Association for Geriatric Psychiatry published a consensus statement on Alzheimer's treatment in 2006. These medications include acetylcholinesterase inhibitors, ginkgo biloba, NMDA antagonists and several psychosocial interventions (cognitive and behavioural interventions and rehabilitation strategies may be used as an adjunct to pharmacological treatment, especially in the early to moderately advanced stages of disease).

A large number of potential treatments for Alzheimer's disease are currently under investigation, including some compounds being studied in phase III clinical trials. For instance, Xaliproden had been shown to reduce neurodegeneration in animal studies. Tramiprosate (3APS or Alzhemed) is a GAG-mimetic molecule that is believed to act by binding to soluble beta-amyloid to prevent the accumulation of the plaques. Tarenflurbil (MPC-7869, formerly R-flubiprofen) is a gamma secretase modulator sometimes called a selective beta-amyloid 42 lowering agent. It is believed to reduce the production of the toxic beta-amyloid in favour of shorter forms of the peptide. Leuprolide has also been studied for Alzheimer's disease. It is hypothesized to work by reducing luteinizing hormone levels which may be causing damage in the brain with aging.

Vaccines or immunotherapy for Alzheimer's disease, unlike typical vaccines, would be used to treat diagnosed patients rather than for disease prevention. Ongoing efforts are based on the idea that, by training the immune system to recognize and attack beta-amyloid, the immune system might reverse deposition of amyloid and thus stop the disease. Although this strategy appeared succesful in mice, the first human clinical assays had to be stopped: microcerebral haemorrhages were induced by passive immunisation and meningoencephalitis by active immunisation. Work is continuing on less toxic A-beta vaccines.

Modifications to the living environment and lifestyle of the Alzheimer's patient can improve functional performance and ease caretaker burden. Assessment by an occupational therapist is often indicated. Adherence to simplified routines and labelling of household items to cue the patient can aid with activities of

daily living. Also, appropriate social and visual stimulation, however, can improve function by increasing awareness and orientation.

Speaker 3: Professor Charles Duyckaerts

France.

TITLE: *"Alzheimer's disease".*

In the European community, the prevalence of Alzheimer's disease dramatically increase in people over 65 years of age, to reach 12% between 80/84 years and 24% from the age of 85 years.

There are two major characteristics that define AD. The neuropathology includes the formation of senile plaques corresponding to an extracellular accumulation of the amyloid-beta peptide, and the deposition of neurofibrillary tangles (abnormal accumulation of the Tau protein) in the cytoplasm of neurons. The neurofibrillary pathology appears more rapidly than the amyloid pathology which develops later, but these anatomical abnormalities always precede the apparition of the first dementia symptoms.

The senile plaques

The senile plaques correspond to accumulation of A-beta. The physiological function of this peptide is still unknown, but it is normally present in the CSF. The peptide amyloid-beta can be detected either ex vivo by immunohistochemistry, or in vivo by using functional imaging with the Pittsburgh Compound-B (C_{11}-PIB).
Senile plaques are not only made of A-beta peptide and also contain lipids such as cholesterol, revealed by filipin staining, and the cholesterol transporter ApoE. However, it remains technically difficult to detect these lipid deposits. Also, the isoform E4 of the apolipoprotein E appears to be the most significant risk factor of AD. The A-beta peptide is a proteolytic product of the transmembrane protein amyloid precursor protein (APP), whose physiological function is also still unclear. APP is a transmembrane protein partly located in the lipid rafts. APP can be secreted outside the cell by the endoplasmic reticulum/golgi secretory pathway and also recycled inside the cell by the endosomal pathway. This traffic is regulated by SORL1 (sortilin-related receptor). Decreased levels of the SORL1 protein is correlated to an increase in the production of amyloid-beta.
Several mutations of the APP gene have been found to cosegregate with familial Alzheimer's disease, and Alzheimer's-type neuropathology has been reported in transgenic mice bearing the sequence of human APP carrying several of these mutations under various promoters. The biochemical, anatomical and behavioural study of these transgenic mice have already given a good idea of the temporal relationship existing between the various AD symptoms, thus providing an index of the kinetics of the development of the disease. Indeed, these transgenic mice exhibit senile plaques that are very stable over time in 21- to 23-month-old mice. These mice also display:

- Impaired performance in the water maze task and in some other memory tasks.
- Altered long term potentiation.
- No or little neuronal death.
- No or little neurofibrillary pathology.

In an attempt to define the cause of these deficits, several hypotheses have been put forward: the extracellular accumulation of A□ peptide is poorly correlated with the symptoms. A-beta also accumulates in the cell body of the neurons. Intracellular A□ is correlated with the development of the clinical signs, suggesting a causal relationship. On the other hands, A-beta peptides form oligomers. These oligomers induce aberrations in synapse composition, shape, and density, resulting in LTP impairment, which provide a molecular basis for loss of connectivity in Alzheimer's disease.

The neurofibrillary tangles

AD is also a tauopathy: Tau protein aggregates indeed in the neurons during the course of the disease. Tau is a microtubule-associated phosphoprotein mainly expressed in neurons that normally acts to stabilize microtubules. In AD patients, hyperphosphorylated Tau accumulates as paired helical filaments that aggregate inside neuron cell bodies.
While mutations in the tau gene have been linked to neurofibrillary tangle formation in several families of fronto-temporal dementia, no Tau mutations have been described in AD, and transgenic APP mice do not display Tau accumulation. However, aged mice expressing nonmutant human Tau in the absence of mouse Tau (htau mice) developed neurofibrillary tangle formation and extensive cell death, but the presence of Tau filaments did not correlate directly with death within individual cells, suggesting that cell death can occur independently of the neurofibrillary tangle formation.

Taken as a whole, these data support the idea that neurodegenerative diseases such as AD are not primarily due to neuronal death, but instead could result from abnormal accumulation of proteins in the brain.
Alzheimer's disease is an epidemic of very large impact that raises basic and fascinating scientific questions. Various fields of fundamental biology are involved (not only neurosciences) and the questions are specific (they do not deal with neuronal death in general). To go further in the understanding of AD, it seems fundamental to concentrate the efforts on:

- The research material:

- Necessity to plan the clinico-pathologic studies (autopsies) that are too few and too difficult to organize.
- Pathological survey of the population.
- Animal models: lack of facilities.

- The tools (genetics, analysis of proteins, lipids, imaging technology, etc…).
- The search for biomarkers: ligands of lesions (imaging), biological markers for diagnosis and follow up.
- The search for therapeutic perspectives: basic biology (APP, A-beta, ApoE, Tau), enzyme inhibitors, amyloid breakers, inflammation and immunology, etc…

Speaker 4: Professor Giovanni Frisoni

Italy

TITLE: *"Keeping Europe in the mainstream of the fight against Alzheimer's: the search for disease markers".*

In order to better understand the mechanisms leading to the development of a disease, one has to discover the cause as well as the clinical and biological course of the disease. Further, to develop appropriate therapeutic strategies, valid markers of the disease are required. By contrast with AIDS, in which the CD4+ level has been defined as a valid marker to finally lead to clinical trials of anti retroviral therapy, no valid markers of AD have been identified yet.

The first case of what became later known as Alzheimer's disease was described in 1901 by Alois Alzheimer. The clinical syndromic criteria for AD where first defined in 1984 and include a multi domain cognitive impairment with disability which develops progressively and that is not due to other causes (systemic disorders or other brain diseases that could by themselves account for the cognitive impairment encountered). These criteria have lead to the development of symptomatic treatments such as cholinesterase and NMDA inhibitors.

The major cause of AD is the formation of senile plaques corresponding to an extracellular aggregation of the amyloid-beta peptide that is a proteolytic product of the transmembrane APP protein.
In persons who will develop Alzheimer's, the cerebral load of A-beta dramatically increases with age starting from adulthood. For a long period of time (20-30 years) A-beta accumulation gives no obvious symptoms, then, mild memory disturbances start to appear and worsen rapidly (within 4-5 years) into the full symptomatology of AD. This is at this time breakpoint, when the mild cognitive impairment start, that therapeutic strategies have to be developed to restore the deficits.

The search for valid markers of AD focuses on the structural (hippocampus and enthorinal cortex atrophy), functional (PET hypometabolism), biochemical (CSF measures of A-beta and Tau) and molecular (PET of the A-beta ligand C_{11}-PIB uptake) modification associated with AD. This research of valid criteria for the diagnosis of AD will help to develop etiological treatments more effective than the symptomatic ones. A number of drugs are being developed aimed to affect Abeta42 deposition in the brain whose final effect should be the interruption or slowing of cognitive deterioration and some are already in phase III trials, such as gamma secretase modulators and inhibitors, immunotherapy, etc… However, some limitations remain since these diagnostic markers are poorly useful for disease monitoring, the acquisition and processing protocols remain heterogeneous and there is still small case series, short follow-ups, and no data on truly pre-clinical states.

This underlies the need of novel comprehensive programmes for AD, such as the ADNI project (Alzheimer's Disease Neuroimaging Initiative) that started in the USA and which is strongly supported by the NIH and other corporate funds (drug and biotech companies). This project is aimed at validating prospective imaging and biological markers (on the CSF) for use in clinical trials of antiamyloid drugs. ADNI follows for 3 years 400 patients with mild cognitive impairments, 200 with diagnosed Alzheimer's disease and 200 normal controls in about 60 clinical and research laboratories. Strong emphasis is being devoted to accurate harmonization of the methods for collecting images and biological fluids.

In Europe, two projects are being carried out which try to import the ADNI methods. Both capitalize on the network of centres of excellence for research and care of Alzheimer's disease: the EADC (European Alzheimer's Disease Consortium). By importing the ADNI methodology, Europe will be able to remain in the mainstream of drug development of the large pharmacological companies, and the ADNI methodology will be a powerful knowledge base to further probe into the pathophysiology of the disease and develop more accurate markers with even more advanced technologies. The appointed PIs are a group of European young scientists well known in the field of clinical issues, imaging, and biomarkers of Alzheimer's disease (25/31 from ERA-Net countries). It can be expected that investing on them might hold promise also in the very long term.

Two ADNI-like studies have recently been launched in Japan and Australia. They are mainly supported by governmental funds, but investigators will apply for additional funds to companies that are also funding the US-ADNI. Due to the complex management of administrative, regulatory, and methodological issues involved in multinational studies, single nation are more attractive to industry than European multinational studies. Europe has a larger market than Japan or Australia, but if costs outweigh benefits the pharmacological industry might direct resources for drug testing outside Europe.

In conclusion, the immediate challenge of Alzheimer's disease is finding disease markers. ADNI is a platform that is bound to become the international standard, and Europe should take up the ADNI platform on a large scale and use it to search novel disease markers.

Parkinson's disease and other movement disorders

Parkinson's disease (PD) is a degenerative disorder of the central nervous system that impairs the patient's motor skills and speech. Parkinson's disease is characterized by muscle rigidity, tremor, a slowing of movement (bradykinesia) which can lead to an extreme difficulty to initiate movement (akinesia).
The primary symptoms result the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive.

Parkinson's disease is widespread, with a prevalence estimated between 100 and 250 cases per 100,000 in North America, and 1.7% in China (for those aged ≥65 years).
Cases of PD are reported at all ages, though it is uncommon in people younger than 40. The average age at which symptoms begin in the USA is 58–60; it is principally a disease of the elderly. It occurs in all parts of the world, but appears to be more common in people of European ancestry than in those of African ancestry. Those of East Asian ancestry have an intermediate risk. It is more common in rural than urban areas and men are affected more often than women in most countries.

There are other disorders that are called “Parkinson-plus diseases”. These include multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).
Some people include dementia with Lewy bodies (DLB) as one of the “Parkinson-plus” syndromes. Although idiopathic PD patients also have Lewy bodies in their brain tissue, the distribution is denser and more widespread in DLB. Even so, the relationship between PD, PD with dementia (PDD) and dementia with Lewy bodies (DLB) might be most accurately conceptualized as a spectrum, with a discrete area of overlap between each of the three disorders. The natural history and role of Lewy bodies is very little understood.
Patients often begin with typical PD symptoms which persist for some years; these “Parkinson-plus diseases” can only be diagnosed when other symptoms become apparent with the passage of time. These “Parkinson-plus diseases” usually progress more quickly than typical idiopathic PD. The usual anti-Parkinson medications are typically either less effective or not effective at all in controlling symptoms; patients may be exquisitely sensitive to neuroleptic medications like haloperidol. Additionally, the cholinesterase inhibiting medications have shown preliminary efficacy in treating the cognitive, psychiatric, and behavioural aspects of the disease, so correct differential diagnosis is important.

The symptoms of PD result from the loss of dopaminergic cells in the pars compacta region of the substantia nigra. These neurons project to the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway. The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral lateral nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.

The mechanism by which the brain cells are lost in PD may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. This protein accumulation forms cytoplasmic inclusions called Lewy bodies. Latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles – the endoplasmic reticulum and the Golgi apparatus. Certain proteins like Rab1 may reverse this defect caused by alpha-synuclein in animal models.

Most people with PD are described as having idiopathic PD (having no specific and identified cause). There are far less common causes of PD including genetic, toxins, head trauma, and drug-induced PD.

Genetic causes

In recent years, a number of specific genetic mutations (“PARK” mutations) causing PD have been discovered. These account for a small minority of cases of PD, but provide highly valuable insights on pathways which might be altered in PD. In addition somebody who has "idiopathic" PD is more likely to have relatives that also have PD. This suggests the existence of genetic factors predisposing to PD.

Toxins

One theory holds that the disease may result in many or even most cases from the combination of a genetically determined vulnerability to environmental toxins along with exposure to those toxins. This hypothesis is consistent with the fact that PD is not distributed homogeneously throughout the population:

rather, its incidence varies geographically. It would appear that incidence varies with time as well, for although the later stages of untreated PD are distinct and readily recognizable, the disease was not remarked upon until the beginnings of the Industrial Revolution, and not long thereafter become a common observation in clinical practice. The toxins most strongly suspected at present are certain pesticides and transition-series metals such as manganese or iron, especially those that generate reactive oxygen species, and or bind to neuromelanin.
MPTP is used as a model for Parkinson as it can rapidly induce parkinsonian symptoms in human beings and other animals, of any age. MPTP was notorious for a string of PD cases in California in 1982 when it contaminated the illicit production of the synthetic opiate MPPP. Its toxicity likely comes from generation of reactive oxygen species through tyrosine hydroxylation.
Other toxin-based models employ PCBs, paraquat (an herbicide) in combination with maneb (a fungicide) rotenone (an insecticide), and specific organochlorine pesticides including dieldrin and lindane. Numerous studies have found an increase in PD in persons who consume rural well water; and water consumption is a proxy measure of pesticide exposure. In agreement with this hypothesis are studies which have found a dose-dependent increase in PD in persons exposed to agricultural chemicals.

Drug-induced

Antipsychotics, which are used to treat schizophrenia and other psychosis, can induce the symptoms of PD (or parkinsonism) by blocking dopamine receptors.

Parkinson's disease is a chronic disorder that requires broad-based management including patient and family education, support group services, general wellness maintenance, exercise, and nutrition. At present, there is no cure for PD, but medications or surgery can provide relief from lots of the symptoms, improving the life's quality of the patients. Among the diverse treatments, one can note the use either alone or in combination of Levodopa, dopamine agonists, MAO-B inhibitors, physical exercise and deep brain stimulation.
Other treatment methods are currently under evaluation such as stem cell and gene therapy, neuroprotective treatments or neural transplantation.

Speaker 5: Professor Thomas Gasser

Germany.

TITLE: *"Parkinson's disease and genetics".*

Parkinson's disease is a major health problem with so far more that 1,000,000 European affected, a prevalence of 2% in those over 65 years, an incidence expected to rise due to ageing society, and more than 10 billion € of direct health care costs.

PD is merely due to the degeneration of dopaminergic neurons of the substantia nigra, resulting in a global decrease in dopaminergic control of the target striatum (input structure of the basal ganglia). The current treatments include drugs aimed at restoring the dopaminergic control and more recently the deep brain stimulation method (see also below "Speaker 8: Professor Jens Volkmann"). However, these therapeutics have limits since complications (dyskinesia, dementia…) arise after 3 to 5 years.

The major problem research has to deal with for the development of novel therapeutic strategies for PD is the same as in other degenerative brain disease such as Alzheimer's disease. Indeed, the loss of dopaminergic neurons strongly increases during a long period of time (presymptomatic phase) and occurs well before any symptoms can be detected. Therefore, research has to focus on the identification of useful markers of this presymptomatic phase. Accordingly, part of the mechanism by which dopaminergic neurons of the substantia nigra are lost in PD has been identified, since it is accompanied by an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells which forms cytoplasmic inclusions called Lewy bodies.

In the last decade, a number of specific genetic mutations ("PARK" mutations) causing a Parkinson syndrome have been discovered. However, these account for a small minority of cases of Parkinson's disease (10%) and the other 90% correspond to common sporadic PD without any precise aetiology. Among those rare monogenic mutations, PARK1 and PARK4 affect the gene of alpha-synuclein (SNCA) and induce the formation of Lewy bodies, and there is accumulating evidence that common variants in SNCA confer risks for sporadic late-onset PD.

SNCA only account for 2% of the autosomal dominant PD. Importantly, another mutation (PARK8) which affects the gene LRRK2 has been recently identified and is responsible for 7% of the autosomal dominant PD with pleiomorphic alpha-synuclein and Tau pathology. LRRK2 is the most common PD-gene discovered so far and induces a pathology which is the most similar to sporadic PD. It could therefore represent a useful model since PET studies in LRRK2 patients show that changes in metabolic activity and in the dopamine transporter can be detected in the presymptomatic phase before the loss of dopaminergic neurons.

Therefore, it appears primordial in the European research for PD to find new genes and variants, to generate and analyze model systems and to work towards early clinical trials.

Speaker 6: Professor Jörg Schulz

Germany.

TITLE: *"Parkinson's disease: models and mechanisms identification of treatment targets and compounds".*

Currently, there are three major challenges that fundamental and clinical research has to take into account in order to identify novel treatment targets and compounds for Parkinson's disease:

- The need to identify treatments that slow or stop the progression of the disease:
  - To identify the mechanisms leading to neurodegeneration.
  - To create in vivo and in vitro models that are suitable for screening.
  - To create in vivo models which reflect most of the pathological, biochemical and behavioural characteristics of the disease.
  - To identify approaches which allow a better prediction of success in clinical trials (development of biomarkers).
- The need to identify treatments that can restore neuronal function:
  - To better understand the action of endogenous and exogenous neurotrophins.
  - To understand the potential of endogenous stem cells for the replacement of neurons.
  - To understand the integration of stem cells or transplanted cells into a neuronal circuit.
- The need of a rapid translation of preclinical results into clinical studies based on the use of approaches and libraries of drug candidates that are already approved in the clinic for other indications.

The aggregation of alpha-synuclein into dopaminergic neurons of the substantia nigra is the first step for the development of PD that lead to the death of these neurons. Therefore, therapeutic strategies should target this phenomenon because of the known limits of the use of DA-mimetics that operate downstream, when too much neuronal loss has occurred.

Speaker 7: Professor Wolfgang Oertel

Germany.

TITLE: *"Parkinson Syndrome and other movement disorders".*

Movement disorders include a variety of neurological conditions that are, in general, caused by dysfunction in a specific region of the brain called the basal ganglia. There are two basic categories of movement disorders: those exhibiting slow movement, or a lack of movement, and those with excessive movement. The first category is called "hypokinetic" – Parkinson disease being a prime example. The second category is called "hyperkinetic," such as tics, tremor or chorea (writhing movements).
Movement disorders in general are not well known to the average individual, but they are very common, especially in the elderly. The most widely known movement disorder is Parkinson disease, which is second only to Alzheimer disease as the most common neurodegenerative disease of aging. The National Institutes of Health estimate that Parkinson disease affects between 1,000,000 and 1,500,000 individuals in the United States, with some 20,000 new cases diagnosed each year.

Movement disorders is a relatively recent subspecialty of neurology and involves the study and medical management of diseases such as Parkinson disease (PD), dementia with Lewy body (DLB), multiple system atrophy (MSA) or progressive supranuclear palsy (PSP) along with a variety of other conditions that manifest abnormalities of movement (i.e. ataxia, dystonia, Huntington chorea, Wilson disease, myoclonus, tics...). Thus, the diagnosis can often be confusing since there is no objective marker for a specific disease and the optimum medical management is usually achieved by a skilled neurologist trained in movement disorders.

In general, movement disorders are characterized by an alpha-synucleinopathy (especially in PD, DLB and MSA) but also in other cases by a tauopathy (i.e. for PSP, corticobasal degeneration, and frontotemporal dementia). Alpha-synuclein is a soluble protein, that is principally expressed in neurons. In pathological conditions characterized by Lewy bodies (alpha-synucleinopathy),. this protein can aggregate to form insoluble fibrils that are the principal elements of Lewy bodies. Tauopathies correspond to neurodegenerative diseases resulting from the aggregation of the tau protein. Tau proteins are microtubule-associated proteins that are abundant in neurons. These tau proteins are regulated by phosphorylation and the deregulation of this phenomenon (hyperphosphorylation) can result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved in the pathogenesis of Alzheimer disease and other tauopathies.

In addition PD and other movement disorders can be linked to the development of dementias and to sleep disorders such as the rapid-eye-movement (REM) sleep behaviour disorder (RBD) or narcolepsy.

Dementia in Parkinson disease

Dementia is the progressive decline in cognitive function due to damage or disease in the brain beyond what might be expected from normal aging. Particularly affected areas may be memory, attention, language, and problem solving. Dementia is a later development in approximately 25-40% of all patients suffering from Parkinson disease. The risk to develop dementia is higher in PD patients with rigid-hypokinetic type and late onset. Clinical data from Norway have shown that 80% of 70 years-old PD patients have developed dementia after 8 years of survey. Dementia associated with PD typically start with slowing of thought and progressing to difficulties with abstract thought, visuospatial constructional function memory, and behavioural regulation. Hallucinations, delusions and paranoia may also develop.

REM sleep behaviour disorder (RBD) and PD

RBD was first described as a parasomnia involving dissociation of the characteristic stages of sleep. The major and arguably only abnormal feature of RBD is loss of muscle atonia (paralysis) during otherwise intact REM sleep (the stage of sleep in which most vivid dreaming occurs). This loss of motor inhibition leads to a wide spectrum of behavioural release during sleep. This extends from simple limb twitches to more complex integrated movements where sufferers appear to be unconsciously acting out their dreams. These behaviours are often violent in nature and commonly result in injury to either the patient or their bed partner. Injuries range from bruises and cuts to fractures, subdural hematoma and other serious injuries. In contrast, all other aspects of sleep appear similar to normal.
60% of RBD is idiopathic and this includes RBD that is found in association with Parkinson disease and DLB, where it is often seen to precede the onset of neurodegenerative disease. Longitudinal studies in idiopathic RBD have shown that after 12.7 years, 38% of the patients suffer also from PD, and that 7 years later, 66% display Parkinsonism and/or dementia.
The neurochemical bases of sleep disturbances in PD can be attributed to the degeneration of specific brain stem neurons and neurons in the mesocorticolimbic system mostly starting during the presymptomatic phase

of the disease (Braak stage I and II). Also, RBD patients exhibit features of early PD (olfactory dysfunctions, sympathetic cardiac denervation and reduced striatal presynaptic dopamine transporter imaging) as well as neuropsychological deficits similar to those encountered in PD (impaired visuospatial learning or visuospatial constructional dysfunction).

Narcolepsy

Narcolepsy is a neurological condition characterized by Excessive Daytime Sleepiness (EDS). A narcoleptic will most likely experience disturbed nocturnal sleep, which is often confused with insomnia, and disorder of REM sleep, but he may also sleep at any random time even after adequate night time sleep.
Narcolepsy is estimated as many as 3 million affected people worldwide, but surprisingly, 85% of the narcoleptics remain undiagnosed. This is partly because its severity varies from obvious to barely noticeable (some narcoleptics do not suffer from loss of muscle control, while others may only feel sleepy in the evenings), but also because it is often mistaken for depression, epilepsy, or the side effects of medications.
Narcolepsy is a disorder of the orexin neuronal system (neuron and receptors are affected) which is located in the hypothalamus, and it is noticeable that orexin cells in the hypothalamus are also affected in PD.

Thus, it is clear that movement disorders meet sleep medicine, and cohort of patients with sleep disorders associated or not with cognitive impairments might help to identify predictive and diagnostic markers for the conversion to clinical PD, to develop useful indicators for disease progression, or to design clinical trials for neuroprotection.

The need of a better cooperation between fundamental and clinical sciences (translational neurology) for the understanding and treatment of neurological diseases can also be illustrated for progressive supranuclear palsy (PSP) which is a rare neurodegenerative disorder of unknown etiology that involves the gradual deterioration of selected areas of the brain (midbrain and striatal atrophy) characterized by a tauopathy leading to the formation of neurofibrillary tangles. Clinical studies on an atypical form of PSP encountered in Guadeloupe have linked the development of this syndrome to the traditional use of Annonaceae, which is a fruit widely consumed in this region. This fruit contains high annonacin levels, which is a lipophillic inhibitor of the mitochondrial complex I (like MPP+ which is a MPTP metabolite, used in fundamental science to induce parkinsonism syndrome in monkeys). Furthermore, annonacin has been shown in animal models to induce nigral and striatal neurodegeneration and tauopathies, providing a possible explanation for atypical Parkinsonism in Guadeloupe, since it can be deducted from those studies that an adult consuming one fruit or glass of nectar per day accumulates within one year the amount of annonacin sufficient to induce neurotoxicity in animal experiments.

In conclusion, “translational neurology” appears to be the major challenge for a comprehensive and efficient neurodegenerative research in Europe. Expert scientists are available in Europe, patients exist in Europe, lots of infrastructures are also available (data base registry, brain banking, DNA banking system…), but support is little available.

Speaker 8: Professor Jens Volkmann

Germany.

TITLE: *"Deep brain stimulation for movement disorders: state of the art and future needs".*

In the 70's, the mass media featured on the interest of neurocybernetics in life sciences – the best example of this is the success of the fiction entitled "The six million dollar man" at this period. Then, as a consequence of the huge advances in cellular and molecular neurosciences, genetics, etc…, this concept was more and more out of date. However, recently, spectacular advances have been made using stereotaxic surgery for the management of particular symptoms of the advanced Parkinson's disease and other movement disorders (tremor, dystonia), and for the treatment of chronic pain or also affective disorders (clinical depression). This highly sophisticated surgical method in terms of neurotechnology is called "deep brain stimulation" (DBS), and although it is not a curative approach, it has provided remarkable therapeutic benefits and an increase of the patient's life quality for otherwise treatment-resistant movement and affective disorders.

Deep brain stimulation involves the implantation of a medical device called a brain pacemaker, which sends electrical impulses to specific parts of the brain. DBS results in the focal inactivation of dysfunctional nervous tissue by use of a frame system, anatomical references and physiological guidance (stereotaxic surgery).
The DBS system consists of three components: the pulse generator (IPG), the lead, and the extension. The IPG is a neurostimulator which sends electrical pulses to the brain to interfere with neural activity at the target site. The lead is a coiled wire insulated with four electrodes and is placed directly at the target site. The lead is connected to the IPG by the extension, an insulated wire that runs from the head, down the side of the neck, behind the ear to the IPG, which is placed subcutaneously below the clavicle or in some cases, the abdomen. The IPG can be calibrated to optimize symptom suppression and control side effects.

DBS leads are placed in the brain according to the type of symptoms to be addressed. For essential tremor and Parkinsonian tremors, the lead is placed in the thalamus. For dystonia and some symptoms of Parkinson's disease (rigidity, bradykinesia/akinesia and tremor), the lead may be placed in either the globus pallidus or subthalamic nucleus (STN).

Indeed, although the Parkinson's disease results from a loss of dopaminergic neurons in the substantia nigra, the resulting alterations in the activity of the basal ganglia responsible for Parkinsonian motor deficits are merely due to increased activity in the STN.

DBS does not cure Parkinson's disease or other movement disorders, but a number of clinical studies have already shown that this technique can help manage some of their symptoms and subsequently improve the patient's quality of life. At present, the procedure is used only for patients whose motor symptoms cannot be adequately controlled with medications, or whose medications have severe side effects. Its direct effect on the physiology of brain cells and neurotransmitters is currently debated, but by sending high frequency electrical impulses into specific areas of the brain it can mitigate symptoms and/or directly diminish the side effects induced by medications, allowing a decrease in medications, or making a medication regimen more tolerable.

The current research goals therefore focus on:
- Establishing the clinical efficacy and safety for current DBS targets and indications.
- Establishing the optimal targets for DBS.
- Understanding the mechanisms of DBS.
- Improving stimulation technology.
- Extending the indication for DBS.

The major problem to take into account is that for a given patient the electrodes have to be where stimulation causes maximal symptomatic benefit at lowest possible stimulation energy and with little or no side effects. As there are a few sites in the brain that can be targeted to achieve differing results, each patient must be assessed individually, and based on their needs a site will be chosen, mainly with preoperative identification of the neurosurgical target with computed tomography or by magnetic resonance imaging, and using intraoperative electrophysiological mapping and clinical evaluation.

Although DBS has been effective in the treatment of movement disorders and is rapidly being explored for the treatment of other neurologic disorders, and as an important tool for the study of the physiology or the pathophysiology of the basal ganglia, the understanding of its mechanisms of action still remains unclear and continues to be debated in the scientific community. Four general hypotheses currently under investigations have been developed to explain the mechanisms of DBS: depolarization blockade, synaptic inhibition, synaptic depression, and stimulation-induced modulation of pathologic network activity. Also, DBS seems to

have a neuroprotective effect since it increases neuronal survival of dopaminergic cells in MPTP treated monkeys (approximately 20%).

Thus, the optimization of DBS technology for present and future therapeutic applications will depend on the identification of the therapeutic mechanisms of action and this will not be possible with a single research modality.

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