ERA-NET NEURON Cofund2

Foresight Symposium 2023

"Bidirectional brain-body interactions"

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This Foresight symposium is part of the Work Package 8

"**Outreach and interaction activities**"

led by Inserm and CNRS

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Welcome

Dr. Marlies Dorlöchter, DLR-PT - NEURON coordinator (Germany)

Marlies Dorlöchter, as coordinator of ERA-NET NEURON, introduced this Foresight symposium on "Bidirectional Brain-Body Interactions" by welcome addressing all attendants: scientific speakers, researchers from Slovakia and from the Slovak Academy of Sciences, representatives of patient organizations, members of the NEURON Scientific Advisory Board, representatives of NEURON partner organizations, and early career researchers. She highlighted for funding organizations the two main aims of this meeting: (i) to provide an expert overview on "Bidirectional Brain-body interactions", and (ii) to shape the planned Joint Translational Call (JTC) for proposals in this area.

Neuron is a network of funding organizations in the area of translational neuroscience research. Over the years, we have had several projects funded by the European Commission, but all the research that is being done in the context of the Era-Net is funded by the national funding organizations. Neuron has representatives from more than 35 institutions, funding organizations and others, from 30 countries and Australia is the latest addition.

What are Neuron projects?

- An entire program for young scientists because they are in the next generation
- An excellent paper in neuroscience award EPNA that we have give annually
- Neuron had organised some events at the Fence Forum
- Privileged access to Cajal training courses, organization of satellite workshops, and poster sessions in almost all our meetings

Neuron is lobbying at the European Commission to ask more money into this area but also to set up as of 2026 a European partnership on Brain Health in this area. Neuron collaborate with other organizations in the EBRA project with the European brain council, JPND, the Human Brain Project and EBRAINS, and try to find a common common view on things and common activities. Neuron continues to interact with society through educational video clips on brain disorders and other presentations. The topic of "Bidirectional Brain-Body Interactions" emerged from the 2020 update of the NEURON Strategic Research Agenda set up by Neuron Scientific Advisory Board and external experts.

Introduction

Dr. Etienne Hirsch, INSERM (France)

It's important to keep in mind that the brain is not an isolated organ. It is known to be the most imortant organ allowing us to walk, to move, to speak…
But all these actions involve bidirectional interactions with others parts of our body and environment. The two most important aspects of this symposium are as follows:

- Discuss interactions between the brain, the body and the environment
- Discuss the influence of the body and the environment on the brain

Because the subject is so broad, it's difficult for funding agencies to write a call that's broad enough to get enough applications without ending up with an overload of applications and a very low success rate. That's why it's necessary to shape the topic.

The Foresight symposium program has been conceived to offer a lot of different lectures and to integrate as many major brain-body interactions as possible:

- circadian rythm and body
- Interaction between the immune and nervous systems
- Brain-gut axis microbiota
- The impact on the brain of vagus nerve stimulation
- Body representations and mental disorders

The aim is that, at the end of the day patients organizations will be able to help to identify a few priorities.

Circadian rythm and body

Carmen Schröder (STRAS&ND, Strasbourg, France)

1) Circadian Rythms

It's always important to remember that planet Earth rotates around its axis, exposing its inhabitants rhythmically to light and darkness in a circadian fashion. This adaptation to the alternating light and darkness, as well as fluctuating temperatures, has been a necessity for all species on Earth. While humans have chosen darker periods for sleep and lighter periods for wakefulness, this is not the case for all animals. At the core of this discussion lies the concept of sleep-wake rhythms, which are essentially circadian rhythms. Sleep-wake patterns are among the most prominent circadian rhythms, where external time and internal body time must synchronize. However, this synchronization is not always perfect, allowing room for potential desynchronization.

Instances of desynchronization can vary in their impact. In some cases, it may go unnoticed and have little effect. Fortunately, for most individuals, this is the case. However, in situations such as long-distance travel, conflicts between internal and external time can become apparent, leading to what is commonly known as jet lag. If this occurs within one's own country, it is referred to as social jet lag. Adolescents often experience social jet lag, as their internal body time may not align with societal schedules. Despite sleep consuming a significant portion of our lives (almost a third) it is surprising that research in this area is not adequately supported. Sleep is not just about energy restoration; it has been demonstrated in animal models and humans that it plays a crucial role in the elimination of neuronal waste and the reduction of DNA damage accumulation during the night.

2) The importance of sleep and impacts of circadian rythm dysregulation

Sleep's role in brain maturation holds great importance, particularly in neurodevelopment and memory consolidation. During sleep, a process of replay occurs, aiding in the retention of important information while discarding irrelevant details. This enables us to achieve a better signal-to-noise ratio upon waking, leading to clearer thinking. Across various cultures and languages, the adage "night brings advice" reflects this phenomenon of clearing one's mind. In childhood, sleep plays a crucial role in learning processes, while throughout life, it contributes to brain plasticity.

The relationship between sleep, circadian rhythms, and mood is a highly individual experience. Insufficient or poor-quality sleep over an extended period can result in increased emotional sensitivity and irritability. Prolonged sleep disturbances may even make individuals more susceptible to anxiety and depression. Additionally, sleep and wakefulness have significant interactions with immune and hormonal balances.

The consequences of sleep deficit or circadian dysregulation are manifold, affecting individuals of all ages. Firstly, physical effects can manifest. While sleep is often associated with brain function, it influences the entire body. Growth, for instance, is heavily influenced by sleep, as growth hormone secretion peaks during deep slow-wave sleep at night. In cases where children experience sleep disruptions, growth may be stunted, prompting pediatricians to consider sleep as a potential factor.

Disruptions in sleep and wake patterns during early stages can have a profound impact on sensory motor development. Additionally, sleep plays a crucial role in maintaining metabolic balance. Extensive and robust data now firmly establish the link between sleep deprivation and obesity in children, adolescents, and adults. Notably, the Center for Disease Control in America provides impressive findings on the correlation between sleep duration and obesity, which can be accessed on their website.

Moving beyond the physical effects, sleep also exerts significant cognitive effects.

When sleep quality is compromised or there is a disruption in sleep regulation, the initial cognitive function that tends to be affected is attention. It manifests as forgetfulness, such as misplacing house keys or struggling to recall recent conversations with colleagues. If this condition persists over an extended period, it can significantly impact learning and memory, with particular significance in childhood.

Sleep deprivation and deficit also have a notable effect on vigilance and alertness. In the early afternoon, for instance, individuals may experience a dip in their circadian rhythm, leading to some audience members feeling drowsy or even nodding off. When sleep deprivation is present, this decline in alertness is further exacerbated, potentially resulting in hypersomnolence. However, in children, an intriguing phenomenon may occur as they combat subjective sleepiness by becoming hyperactive and constantly on the move. Such hyperactivity in children can be indicative of underlying sleepiness.

Emotional dysregulation, an area closely linked to psychiatry, is another consequence of prolonged sleep and circadian disorders. There is a wealth of data indicating that extended periods of such disorders heighten the risk of developing psychiatric conditions. These conditions can manifest internally as mood and anxiety disorders, or externally as irritability, aggression, and behavioral disturbances. Considering the family component from a systemic clinical perspective, severe sleep disturbances in a single family member, especially children, can significantly impact the overall quality of life for the entire family.

3) Unraveling the complexities of sleep and circadian rhythms in neurodevelopmental disorders

The significance of sleep and circadian rhythm research in the field of neuroscience is underscored by the high prevalence of sleep disorders and circadian rhythm dysregulation in numerous psychiatric and neurological disorders. Extensive data have consistently demonstrated that pre-existing sleep and circadian disturbances elevate the risk of developing psychiatric conditions. This association is particularly well-established for anxiety and mood disorders, and even extends to behaviors such as suicidal ideation.
Taking the exploration further, it becomes intriguing to investigate the effects of removing the biological clock. This involves examining how animals respond when the primary clock mechanism is absent. Such investigations can shed light on the intricate relationship between sleep, circadian rhythms, and various biological processes, contributing to a deeper understanding of the underlying mechanisms involved. In the realm of scientific experimentation, two approaches have been employed to investigate the subject matter. These include lesion experiments and conditional knockout models. Through these models, various findings have emerged, allowing for the quantification of the oscillatory effects on circadian rhythms and the biological clock. Notably, approximately half of the effects were attributed to direct influences via metta naps, rather than relying on melanopsin-based photo transduction. These findings serve as a valuable resource for

predicting the organization of sleep and wakefulness during jetlag when the data is quantified. Animal models have proven advantageous in this regard, as they offer a level of experimental control that allows for the manipulation and elimination of specific functions through techniques such as knockouts and lesions. However, translating these methodologies to human subjects presents a more challenging endeavor.

To investigate the circadian and non-circadian components in humans, specific chronobiological protocols known as modified constant routine protocols are employed. These protocols involve the participation of healthy subjects who enter the laboratory and undergo a normal eight-hour sleep period, followed by 40 hours of sleep deprivation, and finally a recovery sleep phase. Alternatively, in another condition, subjects experience 150 minutes of wakefulness alternating with 75 minutes of darkness where they attempt to sleep, again followed by a recovery sleep phase. This allows for the examination of both sleep deprivation and nap conditions.

In the sleep deprivation condition, the homeostatic process takes precedence due to the significant pressure placed upon it. While the circadian component is present, it is not always easily observable. On the other hand, in the nap protocol, the homeostatic pressure is kept low, allowing the circadian system to be more distinctly revealed.
Recent research in the field of Psychiatry and Neurology has focused on the potential applications of light therapy. These investigations hold great promise in addressing various conditions, including depression, insomnia, Autism Spectrum Disorder (ASD), and Attention-Deficit/Hyperactivity Disorder (ADHD). By manipulating different parameters, researchers aim to improve patient outcomes in these areas.

The primary goal of this line of research is to make practical advancements that directly benefit patients. The belief is that neuroscience should not only seek theoretical understanding but also serve as a means of improving the real world. One compelling example of this approach is a meta-analysis conducted in 2019. This study compared the effectiveness of different treatments for depression, specifically monotherapy using antidepressant therapy versus monotherapy using light therapy, as well as the combination of both approaches. The findings of the meta-analysis were significant. Light therapy, when compared to placebo studies, demonstrated non-inferiority, with a potential tendency toward superiority. This is particularly noteworthy since light therapy is not as widely utilized in clinical practice as antidepressant medications. Furthermore, when examining combination therapies, specifically the use of bright light in conjunction with antidepressants versus antidepressants combined with placebos, a clear superiority of the combined approach emerged. This combination therapy expedited and enhanced reactivity to antidepressant treatment for depression.

Overall, this research represents a highly practical and applied scientific field with significant potential for real-world applications. It offers the possibility of translating scientific knowledge into tangible improvements in patient care. Developmental disorders, such as Autism Spectrum Disorder (ASD), ADHD, intellectual deficiencies, and various learning and communication disorders, have a high prevalence rate, affecting approximately 12 to 18% of individuals. It is worth noting that sleep and circadian rhythm disturbances are prevalent in these disorders, affecting around 30 to 80% of individuals. To advance the field, it is crucial to prioritize the study of sleep and circadian rhythms as primary factors rather than considering them as secondary outcomes within specific disorders. The research conducted at the Center for Autism and Neurodevelopmental Disorders, led by Cilian Clement, adopts an innovative interdisciplinary approach, bringing together experts from clinical,

biological, chemical, and human sciences. With over 30 research teams and a focus on more than 60 conditions, the center aims to explore the real-life implications of their findings, including their impact on children's education and families' daily lives. The main research area of focus is autism, and the application of actigraphy recordings. Actigraphy involves the use of simple wristwatches to monitor wake activity cycles, which are highly correlated with sleep patterns, particularly in young children.

An illustrative case study of a nine-year-old boy with Autism Spectrum Disorder (ASD) reveals challenges in his sleep patterns. His parents report difficulty in putting him to bed at 8:30 PM, as he experiences prolonged periods of wakefulness before falling asleep. He also encounters extended waking episodes in the middle of the night, a common characteristic of autism. Despite this, his overall circadian rhythm seems intact, indicating the disruption May be attributed to a circadian rhythm weakness rather than a severe disorder. Another example, on a more extreme case involving a seven-year-old boy with ASD, intellectual deficiency, and chunk three mutations. In this instance, the circadian rhythms are severely disrupted, nearly abolished.

These examples highlight the significant variations in sleep patterns observed in individuals with autism and emphasize the complex relationship between sleep disturbances, circadian rhythms, and neurodevelopmental disorders.

The distribution of sleep in individuals with neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD), is often erratic and unpredictable. This randomness in sleep patterns is why families emphasize the importance of conducting research on sleep. It is not merely a minor issue for them. Numerous studies have demonstrated that the presence of ASD combined with sleep disturbances leads to worse outcomes in terms of behavior, cognition, and even autism-specific symptomatology. However, many previous studies have not examined sleep in an objective manner, which is something families have been advocating for. A focus group consisting of parents of children with autism in the UK conducted a small-scale study to determine their research priorities regarding sleep. The results revealed that sleep ranked among the top priorities, both concerning the child's sleep itself and the parents' own sleep, which is often affected by the child's sleep difficulties. Similarly, in France, an intriguing development occurred during the full COVID-19 pandemic in 2020. A group of family associations dedicated to children with neurodevelopmental disorders, including autism, ADHD, intellectual deficiency, and genetic syndromes, was formed. They collectively recognized the significance of sleep and decided to make it the focus of their first year of participatory research. This collaborative effort highlighted the shared concern among these associations regarding the impact of sleep on the well-being of individuals with neurodevelopmental disorders.

In this analysis, sleep patterns were measured using actigraphy, and the findings revealed significant associations between sleep and various symptomatology in children. Specifically, 18% of irritability symptoms, 70% of social withdrawal symptoms, and 36% of stereotypical behavior could be explained by sleep and circadian measures. One crucial factor that emerged was the duration of the longest uninterrupted sleep period. Children who slept for a continuous stretch of six hours exhibited better outcomes compared to those who experienced three separate two-hour sleep periods. This difference in the longest continuous sleep episode was highly significant when comparing patient groups with low and high symptom levels.

4) A breakthrough in treatment with melatonin

The impact of sleep disturbances on symptoms in neurodevelopmental disorders is substantial, but understanding the underlying causes and developing effective treatments are crucial. In the case of autism, significant progress was made, in identifying the main mechanism involved. Studies have focused on the pathway of melatonin, including measuring melatonin excretion in urine. These investigations have revealed that approximately two-thirds of children with autism have reduced melatonin secretion at night, and the root cause appears to be related to lower enzyme activity involved in melatonin synthesis from serotonin, particularly the ASM enzyme.

This pathophysiological mechanism provides a clear direction for treatment. With melatonin deficiency being a key factor, C. Shroder team explored the use of melatonin supplementation and collaborated with the European Medicines Agency (EMA) to find a pharmaceutical company interested in producing an extended-release pediatric melatonin molecule. A multicenter international study involving 125 children aged 2 to 8 years, demonstrated not only a statistically significant improvement, but a highly significant effect after three months here against placebo, but even in the two year follow up on longest continuous sleep episode that increased by 77 minutes after three months compared to 25 minutes in the placebo on externalizing behaviors and on quality of life of the families.

This story is a remarkable one as it highlights the successful collaboration between researchers in identifying the underlying mechanisms and the development of a specific molecule to address the deficiency. This achievement has resulted in widespread prescription of the medication in many countries over the past few years.

5) Conclusion

Translational approaches are the most interesting because there are very good animal models for sleep and for circadian rhythms and it can be transferred into human data. Also, light is a very important area which could translate quickly into mechanism. So light, rhythms and translational aspects, would be interesting because it could lead to defining chronotherapeutic protocols for specific disorders. So light therapy is one but also behavioral approaches manipulating sleep or other pharmacological molecules, especially for mental health and mood disorders.

There could be other side effects, for example, there are groups working on food and how food regulates the circadian rhythm. This is what user groups in France suggested and that there should be objective and subjective evaluations of sleep and circadian rhythms which can be done through specific applications. It could be done to other databases that can be used online.

To combine this, can also be used for rare diseases, with databases like GenIDA in France (created in France, but it's an international database). They have several 1000 inputs. The idea was even in genetics to do participative research. So when parents have a child would have a genetic syndrome, they can fill in online questionnaires, but they also have the opportunity to share what they feel is important for their child.

Brain-gut axis including microbiota

Pr. Anne-katrin Proebstel (University of Basel, Switzerland)

What do bacteria in our gut have to do with the brain? It has been observed in neuroimmunology and brain research over the past decades that the difference between a healthy and a diseased brain is not the absence vs. presence of immune cells (immuneprivilege of the brain), but rather that there exists a finely tuned balance of homeostatic vs proinflammatory immune cells that distinguishes a healthy from an inflamed brain. Recently, it has been discovered that the microbiota can influence this system either by directly interacting with the brain through metabolites and the vagal nerve route or indirectly through the immune system. That is precisely what will be discussed in the following, focusing on neuroimmune and neurodegenerative diseases.

1) Brain-gut signaling and the influence of microbiota

It becomes evident that in most brain disease, particularly neuroimmune diseases, there are two predisposing factors involved in disease development. One factor is genetics, as demonstrated by twin studies as well as genome wide association studies in various contexts (IMSGC. *Nature communications* 2019). The other factor encompasses environmental influences (Pröbstel & Baranzini. Neurotherapeutics 2019). In the case of genetics, for instance, when looking at neuroimmunology, it is known that immune-mediated diseases, such as multiple sclerosis, have a genetic component.

Additionally, environmental factors like vitamin D deficiency, smoking, and Epstein Barr Virus infection play significant roles in disease development. However, there has been a rise of immune-mediated brain diseases over the past decades that cannot be explained solely by genetic or known environmental factors. This suggests that other factors have changed over the past decades and have contributed to the rapid increase of these diseases worldwide. One notable change that has occurred in recent decades is the global shift toward a westernized diet. It is well-established that diet directly affects our microbiota. This is where the interplay of nutrition, obesity, and microbiota becomes important. It is fascinating to contemplate about the significance of microbiota. When we examine the human body, we realize that we are composed of only 50% human cells and 50% microbial cells. This is not merely a philosophical question about our humanity; it highlights the fact that these microbial organisms are not just cellular components. They also contribute a significant amount of genetic material, with more than 99% of our genetic material originating from microbial organisms rather than our human genomes. This indicates that microbiota likely have a profound impact on our overall functioning, including how our brains function or malfunction. Understanding this relationship is crucial for both healthy individuals and those with diseases.

So, if we discuss the broader mechanisms of how our gut and microbiota interact with the brain, one notable connection is the structure of the vagus nerve. Further, it is conceivable that in the context of disease, microbiota may directly influence the brain by translocating from the gut through the bloodstream. Additionally, metabolites produced by microbiota can potentially act on the brain via the bloodstream. Furthermore, one of the significant areas of research and interest lies in understanding how microbiota interact with immune cells, which then travel through the blood to the brain. Over the past few decades, the field of microbiome research has evolved. Firstly, epidemiological data has indicated its relevance. Secondly, there have been significant technological advancements in two areas. One is the advent of advanced sequencing technology, allowing us not only to identify the presence of different bacteria but also to analyze the entire genomic

composition. This provides insights into the functional aspects of microbial organisms, going beyond taxonomy and into their roles and behaviors. Moreover, novel technologies now enable the examination of fungi and viruses, expanding the understanding of microbial components beyond bacteria. With the emergence of new single-cell technologies, it's now possible to study the functional aspects of microbiota and immune cells and their interaction on a single-cell level, which is an intriguing prospect. Additionally, we now have germ-free model systems that allow us to mechanistically study patient microbiota compared to controls and gain insights into their functioning.

2) Unraveling the role of microbiota in multiple sclerosis

Pivotal experiments that shed light on the role of microbiota in MS came from an animal model. In this neuroinflammation model, when antibiotics are administered or the mice are raised germ-free (without microbiota), they exhibit less severe or no diseases (Ochoa-Repáraz et al. *Journal of Immunology* 2009; Berer et al. *Nature* 2011). This demonstrates the fundamental impact of microbiota on disease development.

Furthermore, in recent years, research has shown differences in the composition of gut bacteria between MS patients and controls. While the differences are not dramatic, there are variations in the abundances of certain microbiota that are associated with MS. To overcome inter-individual differences in microbiota and gain disease-relevant insights, international consortia are being formed. These collaborations aim to study microbiota in MS patients and have already replicated previously identified changes in microbiota associated with the disease. With the advancements in sequencing technology, researchers can now explore not only the composition of microbiota but also their functional aspects, including metabolic pathways. Another important consideration is that the biggest driver of microbiome differences between individuals is not necessarily disease-related but rather factors like household and age (Zhou et al. iMSMS Consortium. *MSJ* 2020). Factors such as age and household, even in healthy individuals, shape certain commonalities in the microbiome. Therefore, it is crucial to recruit healthy household controls from the same household when studying MS patients to minimize confounders. Larger studies involving different countries and diverse populations are essential for a comprehensive understanding of these factors, including diet and other confounders. In the context of MS, it has been demonstrated that not only disease onset but also different activity and progression states are associated with distinct microbiota compositions. This presents an opportunity to investigate how microbiota at different disease stages may modulate the condition by carefully selecting well-characterized patient cohorts. Regarding the chicken-and-egg question of whether a genetic predisposition alters microbiota, leading to the disease or if immune dysregulation precedes changes in the microbiome, we do not have a definitive answer yet for MS or any other neurological diseases. However, studies using mouse models have provided some clues. Transplanting microbiota from MS patients compared to healthy controls into mice with an MS-like disease has shown that the mice with MS-associated microbiota experience more severe disease progression. This suggests a possible directionality, implying that microbiota associated with MS might drive the disease. In summary, investigating the interactions between gut microbiota and the brain in MS and other diseases has provided valuable insights into disease development, stages, and potential mechanisms. Further research, international collaborations, and comprehensive study designs are crucial for a deeper understanding of these complex relationships.

3) Microbiota's influence on neurodegenerative diseases and therapeutic approaches

Recent research has shed light on the role of gut microbiota in regulating compounds that impact neurodegeneration in the brain. Fascinatingly, studies using germ-free animals have revealed that the absence of microbiota prevents the development of certain diseases, drawing intriguing parallels. Conversely, when microbiota from Parkinson's patients are introduced into mouse models, it exacerbates the disease (Sampson et al. *Cell* 2016), further supporting this concept. These findings provide the tools to investigate the intricacies of these diseases by examining them mechanistically in patient models. The next step involves devising strategies to treat patients based on this knowledge. Notably, research in Alzheimer's disease has uncovered a compelling link between microbiota, particularly found in the mouth, and the production of specific toxins by *Porphyromonas gingivalis (*Dominy et al. *Science advances* 2019). These toxins increase the deposition of amyloid in the brain and directly contribute to neuronal toxicity. In summary, our understanding of how microbiota modulates neurodegeneration is advancing, presenting exciting possibilities for therapeutic interventions. By exploring these avenues further, we can strive to develop effective treatments for patients.

This research group has developed a small molecule specifically designed to neutralize toxins produced by the bacteria. Remarkably, in animal models, this molecule effectively reduced the likelihood of developing neurodegenerative symptoms. These findings highlight the potential impact of targeting bacterial toxins and provide hope for future therapeutic approaches.
These information from various fields contribute to our conceptual understanding of the complex relationship between microbiota and neurodegenerative diseases. It leads to examining more deeply the mechanistic aspects and investigating the underlying mechanisms connecting microbiota and the brain. It is crucial to consider the directionality of this interaction.

It is also, important to acknowledge that there are still open questions that need to be addressed. When differences are observed in gut microbiota, researchers refer to it as dysbiosis, which occurs in disease states. It is noteworthy that conditions involving the immune system, such as multiple sclerosis (MS) or other neurodegenerative diseases like Parkinson's, have distinct mechanisms. One important mediator between the gut and the brain is the immune system. It is conceivable that microbiota influence the immune system, promoting a pro-inflammatory state that ultimately affects the brain. Additionally, in the context of immune diseases, the concept of molecular mimicry comes into play. Overall, these findings highlight the intricate relationship between microbiota and neurodegenerative diseases. By considering the immune system's role and exploring potential mechanisms, we can further our understanding of this connection.

Regarding neuroinflammation, the question arises: Does the microbiota's influence on the brain result solely from modifying the inflammatory environment in the body, or does it specifically manipulate the immune system to cross-react with brain-related elements? Fascinating data focused on neuroimmunology, specifically studying MS patients and animal models of the disease, identified bacteria carrying mimics that resemble brain proteins (Miyauchi et al. *Nature* 2020). These mimics can trigger cross-reactive immune cells to infiltrate the brain and initiate an immune response. Similarly, further important research demonstrates that immune cells in the gut can be primed differently than those in other locations (Hiltensperger et al. *Nat Immunol* 2021), underscoring the role of microbiota in this process.

It is worth emphasizing that the current focus in the field is predominantly centered around the gut. However, this discussion highlights the need to broaden our perspective and explore the intricate connections between microbiota at other mucosal sites, the immune system, and brain function.

The gut harbors the largest population of microbiota, but it's worth noting that microbiota also exist on our skin and in other areas of our body. Evolving data suggest that microbiota in these alternative sites can also influence the immune system and impact brain-related disorders (Hosang et al. *Nature* 2022). Exploring these novel avenues is essential and warrants further investigation in patient populations. Conceptually, when considering how microbiota modulate the immune system, there is potential to engineer microbiota to address pertinent questions and potentially utilize them as therapeutic agents. The research group of Anne-Katrin Pröbstel, although unpublished, focuses on understanding potential similarities between microbiota and brain proteins that could trigger immune cells to cross-react with the brain. In line with this, they have engineered bacteria that display a brain protein mimic on their surface and administered them to mice predisposed to developing multiple sclerosis (MS). The results reveal an accelerated disease course in mice exposed to bacteria with the brain protein mimic, indicating that molecular mimicry may drive this phenomenon. In this case, immune cells in the gut become activated by the bacteria and subsequently cross-react with the brain, highlighting a potential mechanism. Currently, they are exploring the possibility of engineering these microbiota to elicit beneficial immune responses. This example shows how a broader understanding of these concepts can help identify avenues for therapeutic intervention.

4) IgA B cells in neuroinflammation and microbiota Interaction

Shifting focus to another topic, specific immune cells found in the gut, known as IgA B cells, are of particular interest. These B cells reside in the gut's lamina propria and play an essential role in maintaining everyday functionality of the microbiota (Neziraj et al. EJI 2023). They contribute to homeostasis and the maintenance of microbiota. This aspect is particularly relevant in the context of the gut. The interest lies in understanding the role of specific cells, known as IgA-producing B cells, in the context of neuroinflammation and multiple sclerosis (MS). As microbiota vary across different body sites, it is natural to consider their potential role in this process. Thanks to collaborative efforts with other researchers, an intriguing discovery has been made. Both in MS patients and in animal models (Pröbstel et al. *Science Immunology* 2020; Rojas*, Pröbstel* et al. *Cell* 2019), it has been observed that these IgA-producing cells, which are typically associated with maintaining gut homeostasis, did not remain confined to the gut during neuroinflammation. Instead, they migrated into the spinal fluid and, surprisingly, were also found in brain tissue, as confirmed by autopsy findings from MS patients. Naturally, the question arose: What is the purpose of these cells in the inflamed brain? Interestingly, it has been found that these cells exhibited specificity to microbiota, indicating that they did not cross-react with any brain components. When examining their function in both animal models and tissue samples, researchers discovered that these cells possessed regulatory properties.

These findings suggest that the migration of IgA-producing B cells into the inflamed brain is a phenomenon worthy of further investigation. While these cells do not seem to recognize brain-related elements, their presence and regulatory function raise intriguing questions about the interplay between microbiota, immune cells, and neuroinflammation.

5) Microbiota's impact on brain function: current insights and future prospects

In summary, data published by Anne-Katrin Pröbstel's research group suggests that IgA-producing cells, which reside in the gut of all individuals, play a crucial anti-inflammatory role in the context of

neuroinflammation. These cells may also have a role in protecting the brain from low-grade microbial translocation. They have explored whether this phenomenon is specific to multiple sclerosis (MS) or if it has broader implications for how the immune system regulates inflammation. Interestingly, they found similar anti-inflammatory cells in other neuroinflammatory conditions, and they are now investigating their presence in systemic inflammatory diseases as well. By examining various disease contexts, we can gain valuable insights and unravel important shared concepts across diseases that can be discussed further. To better understand immune cell trafficking of both pro-inflammatory and anti-inflammatory cells from the gut to the brain further studies are currently conducted in blood and spinal fluid samples of patients. This allows us to examine the trajectories of these immune cells in well-characterized patients. Simultaneously, researchers can investigate microbial triggers in mouse models using patient-derived materials such as stool samples. Another important topic to address is the concept of "leaky gut," which is of great interest to patients and the general public. However, it is crucial to note that our understanding of this phenomenon is still in its early stages across various fields, including infectious diseases, inflammatory diseases, and autoimmune diseases. Technically, it is challenging to make definitive statements about sequencing microbial populations from the blood or the brain. Hence, we must approach the topic of leaky gut with caution and recognize that more research is needed to draw definitive conclusions.

Lastly, mounting evidence points to a key role of microbiota in mediating therapeutic response and side effects in various immune-mediated conditions treated with immunomodulatory agents including MS (Diebold et al. Gut microbes 2022) (Figure 1). These data raise fundamental questions about understanding the interplay between microbiota and immune modulatory therapies in neuroinflammatory diseases and beyond.

Foresight symposium 2023

Proprioception alteration and CNS plasticity

Fosco Bernasconi (EPFL, Switzerland)

Despite Parkinson disease (PD) is excluded from the topic of Eranet NEURON funding, it will be taken as an example of proprioception alteration in brain pathologies. PD, defined as a motor disorder, has three main motor symptoms: bradykinesia, rigidity and tremor. However, there are many non-motor symptoms that appear years or sometimes decades before the onset of motor symptoms, making them of great interest as prodromal markers of the disease.

Among these non-motor symptoms, 50% of the patients suffer from hallucinations and as the disease progresses, this percentage rises up to 70 - 80%. As hallucinations are associated with other symptoms such as psychosis and cognitive decline, they may suggest a more severe form of the disease.

There are two types of hallucinations in PD. The first type is minor hallucinations, including presence hallucinations (the feeling that someone is behind you when there isn't), which are one of the earliest and most common hallucinations in PD. Then there are more complex visual hallucinations. Returning to the symptoms of PD, complex hallucinations are closely associated with dementia. However, using complex hallucinations as a marker of dementia is not appropriate, as they usually occur at an advanced stage of the disease. Knowing the progression from minor to complex hallucinations, there is a proposal to use minor hallucinations as an early marker of microcode cognitive impairment and, ultimately, dementia. So, the objective is to have methods and procedures in place to systematically investigate and possibly identify at a very early stage those patients who are likely to have hallucinations in the future to know which patients will have a more severe form of the disease, characterized by dementia and cognitive decline. Another problem with hallucinations is that they are highly subjective and private experiences. The patient must therefore interpret the hallucination as an association and report it correctly to the clinician or scientist, and the scientist must interpret it to finally classify it. This is known to be a source of bias at every stage, making investigation even more difficult. The problems associated with self-reporting stems from patients' fear of being stigmatized as schizophrenic. But subjective reports are impossible to verify quantitatively, so another method and procedure are needed.

Researchers therefore have several methods at their disposal for inducing hallucinations. For example, basic brain stimulation, which is generally performed on epileptic patients is a classical method. There is also epileptic monitoring, where sometimes, depending on the region, the clinician stimulates different electrodes.

Another method is to use a robotic system, which has two components. A frontal robot, where the participant is asked to perform a repetitive movement with his finger, and these proprioceptive and tactile signals come into play. These thought movements are reproduced at the back by the second robot, either in synchrony or in asynchrony. The last has proven to induced presence hallucinations under safe controlled experimental conditions.

What this method has also shown, is the possibility to reproduce the impression of a presence that is characteristic of hallucinations in PD. The next step in this experiment is to check whether this method is also valid for PD, and whether patients with symptomatic resonance, i.e. who have hallucinations at home, could induce a strong hallucination of presence using the robot.

An experiment was conducted using a psychophysical approach, in which different delays between movement and touch on the back were introduced. Participants were asked to perform a few box movements and then indicate whether they had experienced the illusion. At zero millisecond delay, patients suffering from presence hallucinations in everyday life showed a strong tendency to feel the induced presence hallucination. Furthermore, they found that presence hallucination was modulated by sensorimotor conflict, with increased conflict leading to more pronounced presence and resolution. This initial pilot study is now being replicated in a multi-center study across Switzerland involving a large cohort of patients patients, and they are also incorporating fMRI during the task to gain further insights. The participants are blindfolded, and when someone tries to isolate himself from the environment to distract him from the experiment, several patients were surprised to see that someone was a few meters away from them and in front of them, but they had the sensation that someone was there and touching them on the back. This makes it quite convincing that induce something in the right direction with this robotic sensory-motor stimulation, is similar to what they have in their daily lives at home. The robotic system was adapted to a fMRI scanner to implement the same system with a front robot and an attached robot. During the sensory-motor task involving motor proprioceptive and tactile stimuli, particpants reproduced the effect despite the presence of strong tactile proprioceptive stimuli.

The brain scans revealed a significant fronto-temporal sensorimotor network associated with presence hallucination in healthy participants. To ensure that this network is also relevant for clinical cases, 11 patients with neurological issues like stroke or epileptic lesions who had experienced presence hallucinations were examined. By mapping the brain lesion network in these patients, the temporal insular region was identified as a key region for presence hallucination in neurological cases. Overlaying the results from the robot induced sensorimotor hallucination with the neurological patient data led to the identification of an extended fronto-temporal network shared between the two datasets, validating the common presence hallucination network in PD. Resting-state fMRI data from PD patients at San Pau Hospital of Barcelona some who had presence hallucinations and some not, showed that the functional connectivity of this network enabled to classify patients according to whether or not they had hallucinations. The classifier's performance was mainly influenced by the fronto-temporal network disconnection. These results indicate that patients with the lowest functional connectivity were more likely to experience presence hallucinations. The fronto-temporal disconnection aligns with the hypotheses and models proposed for schizophrenia, specifically the impairment in the four walls model. Thus, when an action is generated, predictions are made about its outcome. If the predictions match the sensory stimuli we receive, everything is considered self-generated and normal. However, if there is a mismatch between the predictions and the stimuli received, under certain conditions the action may be perceived as not being self-generated and may eventually lead to the presence of hallucinations.

Conclusion:

Several projects related to hallucinations in PD are ongoing. For instance, they are also exploring real time neurofeedback using advanced fMRI analysis to modulate the network associated with presence hallucinations, with the aim of increasing sensation in healthy subjects and reducing activity in

patient trials. This non-pharmacological therapy aims to offer a safer and more effective treatment for PD, avoiding the serious side effects of antipsychotic drugs.

Virtual reality is also being used to induce complex visual hallucinations at different stages of the disease, thus addressing hallucinations at different stages of the disease. Addressing hallucinations and cognitive decline from different angles with technical approach to diagnosis and treatment is therefore a promising research axis.

Vagus nerve stimulation and impact on the brain

Kroemer Nils (University of Bonn & University of Tübingen, Germany)

This topic aims at understanding the impact of vagus nerve stimulation on the brain and identify changes that could be achieved through non-invasive stimulation. This knowledge is crucial when considering broader applications of vagus nerve stimulation, especially at early stages of diseases. Invasive vagus nerve stimulation has already been employed for treatment-resistant depression and epilepsy, but exploring non-invasive alternatives can extend its potential benefits to a wider population. The aim is to develop a treatment that can be used during the initial phase of depression, in conjunction with psychotherapy. Here, the goal is to understand how vagus nerve stimulation affects brain-body interactions and explore potential mechanisms. In addition, the neurobiological and behavioral markers that could serve as indicators of stimulation efficacy are being investigated. Optimizing the application of non-invasive vagus nerve stimulation relies on the identification of reliable biomarkers, essential for assessing its efficacy independently of the results of clinical trials.

1) **The neurocircuitry of gustastory reward and the impact of vagus nerve stimulation**

A 2018 study identified a neurocircuit for gustatory reward, with invasive stimulation of the right nodose ganglion of the vagus nerve conditioning preferences for flavors and food-associated places through dopamine release in the midbrain and striatum (Han et al., 2018). In comparison with stimulation of the left nodose ganglion, it showed stronger dopaminergic effects on the right side, suggesting lateralization. Non-invasive vagus nerve stimulation research has mostly focused on the left ear to avoid potential cardiovascular side effects, but right-sided non-invasive stimulation at the ear can be considered equally safe by now. Also, the literature has provided insights into the pathways stimulated by vagal afferents, emphasizing negative homeostatic feedback signals from the brainstem to other regions in the brain. Interestingly, there are separate subpopulations within the nucleus of the solitary tract, influencing food intake by either increasing or decreasing it (Chen et al., 2020).

Vagal efforts are also involved in the memories and this contributed to the idea of a low road to desire when people are thinking about food choices.

Humans taste buds have an undeniable preference for delicious, calorie-dense food, because of the subconscious and instinctive inclinations. These preferences are largely influenced by subliminal reward signals emanating from our gut, constantly shaping our choices. The gut keeps a watchful eye on the caloric density of the food we consume, updating our brain's representations accordingly.

Yet, when it comes to decision-making, conscious representations also play a significant role and higher-order cortical areas in our brain come into play, prioritizing long-term goals such as healthiness. Similarly, sustainability of food choices emerges as another long-term consideration, guided by understanding and a model-based approach. On the other hand, a reflexive mode operates effortlessly, prompting people towards comfort meals. This reflexive mode, associated with choices and vigor, operates automatically, and motivates people's actions. However, maintaining the reflective mode can be a challenge. Though urged to use this mode for better food choices, it demands continuous attention and cognitive effort. Buffets are good example for the trade-offs as we oscillate between taste and other considerations. For those striving to shed pounds, adopting the reflective mode may be advised, but maintaining it effectively is limited by our cognitive capacity for conscious decisions.

So, a complex interplay of subconscious, reflective, and reflexive modes shapes the preferences, and challenge people to strike a balance for better and healthier decisions.

Now, the idea is that we can target this pathway to subconscious pathway by stimulating a part of the ear, which is the so-called auricular branch of the vagus nerve.

The fundamental question here revolves around the similarity of signals elicited in the brainstem and whether they activate a comparable cascade, that allow to target this circuit. This inquiry traces back to data from two decades ago, where it was discovered that stimulating the cymba concha area with an electrode triggers specific potentials from the brainstem. In contrast, stimulating other parts of the ear does not yield the same effect. Based on these findings, a widely adopted stimulation device was designed, commonly used in various studies. This device offers the advantage of simultaneous use with behavioral recordings and functional neuroimaging, enabling acute vagus nerve stimulation and allowing researchers to investigate resulting brain changes.

Focal stimulation holds great promise, mainly due to its ability to target a relatively small region in the brainstem. However, the significance lies in the fact that these nuclei in the brainstem have a remarkable capacity to influence a wide range of nerve transmission systems. Unlike being specific to just one system, they can trigger changes across the entire brain and effectively modulate large-scale cortical activity. This versatility makes focal stimulation a powerful tool with the potential to impact various neural processes throughout the brain.

One popular example for monitoring release of noradrenaline is pupil dilation, because it is very easy to measure and there's also good evidence from animals that this works. Researchers have tried a lot of different settings, and the main finding is that higher stimulation intensity leads to stronger pupil dilation. One interesting thing about this is also that it showed that part of the effect is dependent on cortical release of acetylcholine so it’s not only triggering phasic noradrenaline release, but downstream, this is also leading to critical release of acetylcholine, which accounts for part of this association between the effects of vagus nerve stimulation and the effects on pupil dilatation (Mridha et al., 2021).

2) What is the consequence of a stimulation at the ear on the rest of the body?

Is it possible, for example, to modify the speed of the digestive path? What about the communication with the brain? To investigate this question, an older technique was used, known as electrogastrography. Like an electrocardiogram, this method involves placing electrodes over the stomach area to monitor and analyze the signals involved in the digestive process. The non-invasive recordings from the Electrogastrography (EGG) confirmed that non-invasive vagus nerve stimulation effectively reduced the frequency of pacemaker cells involved in the digestive process (Teckentrup et al., 2020). Additionally, an independent study conducted with invasive recordings during surgery also showed a decrease in frequency with non-invasive vagus nerve stimulation (Hong et al., 2019b). These results align with researchers’s observations in the non-invasive setting, providing further evidence of the stimulation's efficacy.

3) What about the communication with the brain?

The combination of EGG recordings, functional imaging and vagus nerve stimulation allowed Nils Kroemer’s team to gather comprehensive data and insights during the research process. They tried to

replicate the gastric network which worked so they were able to replicate the functional topography of the gastric network in their sample. Then they looked at the effects of vagus nerve stimulation and indeed, they found an increase in synchronization with the signals of the stomach in the brainstem and the nucleus of the solitary tract and in the dopaminergic midbrain. So those are the primary projection targets in the brain and then across also cortical areas. This means that, in areas where there is already a greater concentration of brain on stomach, the coupling between stomach and brain has been strengthened by stimulation of the vagus nerve (Müller et al., 2022).

4) What about the heart?

The investigations of EEG-associated changes related to a heartbeat analyzed by comparing vagus nerve stimulation show a distinct difference in the evoked potential, likely localized to the insula (Poppa et al., 2022). Although EEG localization can be challenging, two reports have suggested that vagus nerve stimulation might also influence heart evoked potentials. Nevertheless, recent findings challenge the idea that vagally mediated heart rate variability is a good proxy of vagal tone or vagal afferent stimulation (Marmerstein et al., 2021; Wolf et al., 2021).

5) Anti-inflammatory and antidepressive Effects of non-invasive vagus nerve stimulation

There are now a couple of studies suggesting also anti-inflammatory effects of noninvasive vagus nerve stimulation in animals and in humans (Borovikova et al., 2000; Hong et al., 2019a; Wu et al., 2023). Improved mood after acute stimulation exists (Ferstl et al., 2022), but surprisingly, this hasn't been much studied. What has been studied more often are antidepressive effects, also of noninvasive stimulation. Furthermore, a lot of those trials are still comparatively small. Yet, they suggest that the antidepressive effects are at least comparable also to invasive vagus nerve stimulation (Tan et al., 2023). In other words, there doesn't seem to be a strong reason to prefer invasive vagus nerve stimulation, which also comes with a lot of undesirable side effects due to the surgery and may cause loss of the voice of the patient and problems.

6) What kind of ideas are still out there for the future?

Closed loop setups could be something where the stimulation is triggered depending on an environmental input. But it could also be triggered according to signals from the body. Also, personalized stimulation is a unique challenge specific to vagus nerve stimulation which has emerged. In this context, recent research using 3D models of vagal fibers revealed unexpected findings. Yet, in vivo when placing an invasive vagus nerve stimulation device, that target specific fiber bundles to elicit desired effects some patients do not respond as expected, despite targeting the same fiber bundles across participants. This variability seems to stem from individual differences in how these fibers merge and split beyond the electrode placement, resulting in different brain stimulation effects. To address this issue, optimized imaging protocols like optical or ultrasound imaging may provide valuable insights, but these methods have not been thoroughly explored. Notably, direct brainstem activation readings indicate that around 20 to 25% of participants show limited increases in activation (Teckentrup et al., 2021). The same non-response rate is observed in many behavioral measures, likely due to anatomical variations that could affect the effective stimulation of desired fibers.

Conclusion:

In conclusion, vagal afferent stimulation leads to strong activation in the brainstem, and downstream regions likely play a role in explaining behavioral effects. However, further research combining stimulation with tasks and behaviors is needed to dissect these mechanisms effectively. The good news is that this stimulation appears to be effective across different labs and stimulation protocols. Brain activation, pupil dilation, changes in stomach-brain coupling, and gastric frequency all suggest vagal modulation, supporting the idea of eliciting gut-based reward signals and corresponding sensations.

There are also potential associations with heart evoked potentials, although heart rate variability remains a somewhat tricky measure of vagal tone. Regardless, modulating vagal afferent signals can be a powerful tool to modify behavior and improve symptoms by altering interoceptive signals integrate in the brain. This versatility may explain the wide range of ideas regarding the potential of external stimulation.

Body representations and mental disorders

Matthew R. Longo (University of London, UK)

In the case of body dysmorphia, people fixate on a part of their body that they consider ugly or hideous in a way that others don't seem to be able to understand. There are also fascinating differences between the sexes, for example, many teenagers and young men suffer from disorders such as muscle dysmorphia, which leads them to think they're not muscular enough

1) Body representations in psychiatric disorders

Despite patients not experiencing sensory motor problems, there are still observable alterations in the brain networks controlling sensory motor functions in the limb, which seem to be linked to a distinct feeling in the limb. One prominent example is eating disorders, such as anorexia or bulimia, where patients exhibit remarkable body image distortions. For decades, studies have measured perceived body size in these patients, consistently revealing that individuals with anorexia and bulimia tend to overestimate the width of their bodies compared to control groups. This discrepancy persists even when others see them as emaciated. This phenomenon has attracted considerable research interest, leading to numerous studies exploring the underlying mechanisms behind these body image distortions.

Various studies have focused on more implicit tasks involving sensory motor control of the body in individuals with eating disorders. These investigations have revealed that patients tend to overestimate body width in certain situations. For instance, when people walk through an aperture, they subconsciously adjust their body's orientation based on the perceived width of the opening. Healthy individuals usually leave about an extra 20% of their body as a safety margin, whereas patients with anorexia demonstrate an even larger margin of safety. This suggests that their sensorimotor control of walking implicitly treats the body as wider than it is. These findings highlight the interplay between sensory perception and motor control in the context of body image distortions.

On another ground, the phenomenon of phantom limbs in neurological disorders has fascinated researchers for centuries. Going back to the 16th century with the work of Ambroise Paré, individuals who have lost a limb due to an accident or amputation often report vivid subjective experiences of the limb's continued existence. This intriguing observation suggests that there is a central representation or model of the limb in the brain that remains intact, even though the physical limb is no longer present. The brain still perceives and maintains the representation of the limb, causing the subjective experience of its presence. Moreover, residual inputs from the nerves in the stump of the amputated limb play a significant role in shaping the perception of the phantom limb, which can change over time and lead to phantom limb pain.

In stroke patients, there are fascinating conditions collectively known as "disturbed limb ownership." These conditions manifest in various ways. For instance, some patients deny that one of their limbs belongs to them. Studies dating back to the 1940s and 1950s by *Gerstmann* and *MacDonald Critchley* have explored this phenomenon. In cases of hemiplegia following a stroke, patients may completely reject the ownership of the affected limb. Another intriguing aspect of disturbed limb ownership is when patients claim that one of their limbs has turned evil, describing feelings of dislike and even hatred towards it. In one of their studies, *Errante and coworkers* focused on a specific group of

patients with a condition known as pathological embodiment. What they discovered is a correlation between alterations in the experienced representation of the body and specific brain regions involved in sensory motor control of the hand. These brain regions, located in the postero-parietal cortex and the ventral premotor cortex, are often referred to as « the gasping network » by researchers studying motor control. They play a crucial role in the sensory motor control of the limbs.

In various forms of chronic pain, there are distortions and misperceptions of the body, often resulting in an overestimation of body size, particularly in the affected area. Studies conducted by *Lorimer Moseley* in complex regional pain syndrome have revealed that patients perceive the painful hand as being larger and wider than it is. Additionally, research by *Jenny Lewis and co.* has demonstrated that individuals with chronic pain may exhibit neglect symptoms related to the painful area, where they tend to ignore the space around it. These findings suggest that alterations in sensory motor function play a significant role in chronic pain conditions. Interestingly, there are now innovative approaches to pain treatment that involve discriminative training. This approach focuses on training tactile sensitivity on the affected body part, and it is believed that this may induce plasticity in the somatosensory system, leading to effective pain relief.

2) Distortions of body representation and health

The word distortion doesn't necessarily have a pejorative connotation, as everyone has distorted representations of their body. There are two famous maps of the body and brain, the Foerster and Penfield maps. They both distort the body, but in interesting ways. These somatosensory maps in our brain tend to magnify certain body parts, such as the lips, fingers, and especially the fingertips. This magnification grants us exceptional tactile sensitivity in those areas, enabling us to perform intricate tasks like using a knife and fork or tying our shoelaces. These sensory maps create a more detailed representation of these body parts, facilitating our everyday actions. The distortions in these representations of our body make logical sense, as they correspond to the sensitivity required for specific functions. Similarly, it's possible to explore other intriguing illusions related to the orientation of touches on a single skin surface. In *Fiori and Longo (2018)*, participants were presented with pairs of touches aligned at different orientations on their hands. They were then asked to judge the perceived distance between the two points. The results revealed a fascinating sinusoidal pattern, with distances judged to be largest at nearly 180 degrees of orientation. Each subject showed a specific phase of this sinusoid, indicating a perceptual stretch along the width of the hand relative to its length. These perceptual distortions offer valuable insights into how our brain processes tactile information.

3) Perception of body part weight

Usually when people think about body weight, they think about, how they look or how they feel (fat, heavy…). A hand weighs something like 400 grams is not a light thing, but if a hand is lifted it will feel very light. There are lots of anecdotal reports in the literature of stroke patients with hemiplegia who complain that their hand feels heavy. A study by *Anna Kuppuswamy and coworkers* showed a very interesting association of this with fatigue. They have a scale of limb fatigue that they give to stroke

patients. Then they sorted the patients by whether or not they agreed with the statement « my limbs can become very heavy », and the patients who agreed with this showed reported more fatigue than the patients who didn't. When they looked at an actual measure of how well people were able to function with the hand they didn't show any association with heaviness. The conclusion is that this behavior seemed to be specifically linked with fatigue. Stroke patients who complain that their limb is heavy because of a prosthesis can in fact perceive this weight perfectly accurately. The problem they encounter is that they do not perceive the subtraction of limb weight that seems to occur in everyone. And this perceived heaviness seems to be linked to a lack of integration of the limb with these sensorimotor networks.

4) Emerging aera and priorities for research

A new approach, known as the hoop task, is being utilized by *Keizer and coworkers* to address eating disorders in patients. The task involves using hoops of varying sizes, resembling hula hoops, which patients stand in and attempt to lift across their bodies. Through this activity, patients receive visual, motor, proprioceptive, and tactile information about the hoop's movement around their bodies, providing them with multisensory cues to gauge the actual diameter of their bodies. This visceral experience goes beyond simply looking in the mirror, offering a potentially more effective way to address body image distortions. Likewise, this approach is also being explored for its potential application in managing chronic pain. By integrating various sensory cues, the hoop task aims to provide a comprehensive sensory experience that may prove beneficial in the treatment of both eating disorders and chronic pain.

A few years ago, *Jenny Lewis and co* conducted a fascinating study using an augmented reality system called the Mirage system, developed by Roger Newport. The Mirage system captures a video image of the patient's hand and modifies it to appear less fat than it is. The goal is to present the hand in a way that aligns with the patient's desired perception. However, as the video image is based on real-time, any movement the subject makes with their hand is reflected in the video image. This innovative approach has shown promise as a potential treatment for complex regional pain syndrome. Virtual reality offers a wide range of possibilities for altering the experience of the body. In formal studies, researchers have successfully manipulated various characteristics of avatars, such as weight, age, sex, ethnicity, and body part lengths, while individuals still maintain a strong sense of body ownership over these virtual representations. Despite knowing that these avatars do not correspond to their real bodies, participants can easily embody and feel connected to them.

Conclusion:

To conclude, the phenomenon of people overestimating body width remains consistent across various tasks, but the reasons behind this effect are not entirely clear. A fascinating study by *Saadon-Grosman and co* shed some light on this by applying tactile stimulation to different body parts while subjects were in the scanner. In the parietal cortex, the resulting somatotopic map showed the familiar Penfield homunculus with exaggerated lips and hands but a smaller torso. However, other brain areas exhibited different patterns of body part magnification. At the moment, neuroscientists have no idea of the functional relevance of these different distortion patterns, these different

magnification patterns, how they can be modified in different patient groups and the functional and clinical implications of this.

Panel discussion with representatives of European patients' organizations
Raluca Nica (Gamian Europe) & Orlga Galvin (EFNA)

The Foresight symposium was concluded by a panel discussion with representatives of EFNA and Gamian Europe, providing a patient view on the research on "Bidriectional Brain-Body interactions" and pointing the necessary efforts to improve patients' life.

One of the big question about the discussion was, « how can we increase, encourage patient engagement in the applications? »

Neuron has a review committee made up of patients or patient representatives who judge the quality of applications and do so in collaboration with their part of the review committee. It was pointed out that in France, in the field of autism, researchers are already strongly encouraged to talk directly to patients at the very beginning of the project, and the result is that this is really changing the way studies are conducted, with more inclusivity and equality. However, it was also pointed out that Neuron will probably receive around a hundred applications, and that the risk of this method is to overload patients and their representatives. In addition, the European and international scale of the project will lead to organizational difficulties.

It was to add two more points in the evaluation criteria of the call:

1. Applicants have to mention that will be patient on the Review Board
2. Patients have to be involved in the elaboration of the study

But, it was reminded that in their calls Neuron has already a section saying « The ERA-NET NEURON seeks to strengthen patient engagement in research. » and that « All applications should include a description of expected outcomes with potential relevance for patients. Applicants are expected to engage patients, their care givers or patient organisations as appropriate in the research. Meaningful patient engagement can occur at the level of research planning, conducting research or disseminating research results». It has therefore been suggested that to complete this text, explanations and details should be added on the part of the proposal in which the patient will be involved.

It was also highlighted that there is a risk of discouraging people if patient involvement is mandatory. But participants agreed that without making such involvement compulsory, it would be a good compromise to write a paragraph about how candidates thought about patient involvement and at what stage of the study..

Foresight symposium 2023

Annex

List of Participants

Speakers

Carmen Schröder	STRAS&ND, Strasbourg, France
Anne-katrin Proebstel	University of Basel, Switzerland
Fosco Bernasconi	EPFL, Switzerland
Kroemer Nils	University of Bonn & University of Tübingen, Germany
Matthew R. Longo	University of London, UK

Invited guests

Daniil Grinchi	Slovak Academy of Sciences
Michal Hajduch	Comenius University Bratislava
Tomas Hromadka	Slovak Academy of Sciences
Alzbeta Idunkova	Slovak Academy of Sciences
Lubica Lacinova	Slovak Academy of Sciences
Martin Marko	Slovak Academy of Sciences
Katarína Ondáčová	Slovak Academy of Sciences
Daniela Ostatnikova	Slovak Academy of Sciences
Igor Riecansky	Slovak Academy of Sciences
Peter Valkovic	Slovak Academy of Sciences

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Leszek Kaczmarek	Nencki Institute
Brigitte Malgrange	University of Liege – GIGA stem cell
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