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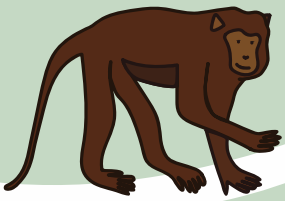

In this issue

ILLUSTRATION:
YASMIN GUERRA

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Beta blues: when oscillations hit a sour note in Parkinson's disease

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Yasmin comes from Brazil. She holds a Bachelor's degree in Psychology and a joint Master's degree in Neuroscience from the University of Bordeaux and Charité Universitätsmedizin, Berlin. She is currently a PhD student at IMN where she studies the neural dynamics of the cortico-basal ganglia-thalamic network in Parkinson's disease.

Abstract

Parkinson's disease (PD) is a movement disorder caused by neurodegeneration of midbrain dopaminergic neurons. Electrophysiology research has highlighted the existence of neuronal oscillations within the beta frequency range in PD animal models and patients, which are supposed to be involved in the disease's motor symptoms. However, those oscillations are also observed in the healthy brain and could have a role in normal motor function. Hence, this review aims to explore the functional role of beta oscillations, their pathological features in PD, and how available treatments could target them to provide therapeutic outcomes.

Keywords

Basal ganglia, beta oscillations, electrophysiology, Parkinson's disease

Abbreviations

6-OHDA – 6-hydroxydopamine

aDBS – Adaptive deep brain stimulation

BG – Basal ganglia

GPi – Internal segment of the globus pallidus

LFP – Local field potentials

GPe – External segment of the globus pallidus

CBGTC – Cortico-basal ganglia-thalamo-cortical loop
cDBS – Conventional deep brain stimulation
DBS – Deep brain stimulation
ECoG – Electrocorticography
EEG – Electroencephalography
PD – Parkinson's disease
MPTP – 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine
SNc – Substantia nigra pars compacta
SNr – Substantia nigra pars reticulata
STN – Subthalamic nucleus
UPDRS III – Motor section of the Unified Parkinson's Disease Rating Scale

Introduction

Parkinson's disease (PD) is one of the fastest-growing neurodegenerative disorders in the world, affecting 0.1-0.2% of the global population at any time. The prevalence increases with age to affect 1% of the population above 60 years old [1-3]. Its main pathological hallmark is the progressive neurodegeneration of dopaminergic cells in the midbrain. Dopamine depletion greatly impairs the functioning of a set of subcortical structures, grouped as the basal ganglia (BG). Together with the cortex and the thalamus, they form the cortico-basal-ganglia-thalamo-cortical network (CBGTC loop), notably responsible for action selection and initiation [4]. Therefore, CBGTC loop dysfunction leads to the movement impairments observed in PD and other movement disorders.

Modern models of the CBGTC loop propose that cortical signals are transmitted to subcortical structures through three distinct pathways: direct, indirect, and hyperdirect [5] (Figure 1).

Those pathways relay signals through different BG nuclei before they reach cortical structures again via thalamic projections.

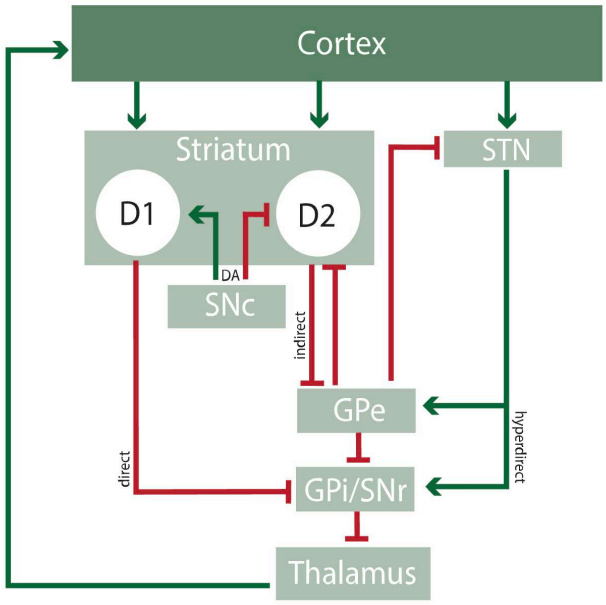

Figure 1. Box and arrow model of the CBGTC loop. All pathways start from the cortex level. In the normal state, the direct pathway leads to disinhibition of the thalamus and consequent cortex excitation, increasing motor activity. In contrast, the indirect and hyperdirect pathways cause activation of GPi and SNr, which inhibit the thalamus, resulting in decreased activity of cortical neurons and suppression of movement. Dopaminergic inputs from the SNc to the striatum reinforce the activation of the direct and indirect pathways, producing an excitatory/inhibitory balance necessary for adequate movement control. In PD, hypoactivation of the dopaminergic system leads to a network imbalance, resulting in weaker cortical activation and decreased movement production. Green arrows: excitatory inputs; red arrows: inhibitory inputs. DA: dopamine; D1: D1-receptor expressing neurons; D2: D2-receptor expressing neurons; SNc: substantia nigra pars compacta, GPe: external segment of the globus pallidus;

GPi: internal segment of the globus pallidus; SNr: substantia nigra pars reticulata; STN: subthalamic nucleus.

In PD, neurodegeneration predominantly affects the dopaminergic neurons of substantia nigra pars compacta (SNc), one of the BG's structures. Dopamine loss disrupts the coding capabilities of BG neurons, as the striatum, one of its input nuclei, is highly dependent on SNc dopaminergic inputs [6]. Based on the pathways model of the BG, researchers suggest that in PD the excitatory-inhibitory balance within the BG could be disrupted, likely leading to an excessive inhibitory drive to the thalamus [7]. This imbalance is thought to cause less activation of cortical structures responsible for motor commands, resulting in PD's core motor symptoms: absence of voluntary movement (akinesia), slowness of voluntary movement (bradykinesia), rigidity, and tremors (involuntary shaking) [8]. Together with non-motor symptoms such as sleep disturbances and gastrointestinal issues [9], also common in PD, the disease can significantly impact a patient's quality of life.

To gain a deeper understanding of what happens in the Parkinsonian brain, one first needs to understand a thing or two about neuronal communication.

Neurons transfer information to each other through electrical signals. Sometimes, electrical activity can follow rhythmic patterns known as neuronal oscillations or brain waves. They are observed as periodic fluctuations in the extracellular voltage, measured by either positioning macro electrodes on the skull or by implanting microelectrodes in the brain. Oscillations can happen at the individual level (single neuron firing at a fixed frequency) or the population level (group of neurons firing synchronously). Depending on the way the raw electrical signal is recorded and filtered we might get different brain activity signatures. For example, preserving only low-frequency components (<250 Hz) results in a slow electrical phenomenon called local field potential (LFP), which probably represents the synaptic input at the recorded region [2]. In contrast, preserving only high-frequency components (>250Hz) results in a fast signal that reflects the spiking activity of a neuron or a population of neurons. We can record spikes and LFPs in behaving animals by inserting microelectrodes in their different BG structures. When it comes to patients, we can record LFPs in their subthalamic nucleus (STN) through deep brain stimulation (DBS) leads, one of the current therapies for PD. Additionally, we can record their cortical activity with electrodes placed on the skull (electroencephalography, or EEG) or placed on the top of the dura mater (electrocorticography, or ECoG).

But why do we need to talk about neuronal electrical activity in PD? Besides dopamine depletion, electrophysiology research has shown the appearance of excessive neuronal oscillations in different BG nuclei of PD patients within the beta band, defined over an extended range of 8–35 Hz [10].

The 6-hydroxydopamine (6-OHDA) lesioned rodents and 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP) treated non-human primates are classic animal models of parkinsonism. Both substances are neurotoxic and degenerate dopaminergic neurons, inducing motor symptoms similar to those observed in PD patients [11]. Beta oscillations are also observed in the CBGTC network of Parkinsonian rodents and primates [12-14], however, they are absent in the early PD stages of those animal models [15-16]. This challenges the idea that they have a causal role in the disease, although divergent findings have been reported [17].

Nonetheless, the strength of the beta signal (known as beta power, see Figure 2) has been correlated with the degree of motor impairment observed in PD patients, and treatments available today decrease beta activity while also

alleviating symptoms. In this context, electrophysiology studies have targeted its modulation to provide more effective treatments for the disease.

Given the assumed involvement of beta oscillations in PD pathology, this review aims to (1) examine the function of beta oscillations in healthy and Parkinsonian brains and (2) analyze how current PD treatments target and influence these oscillations to optimize clinical outcomes.

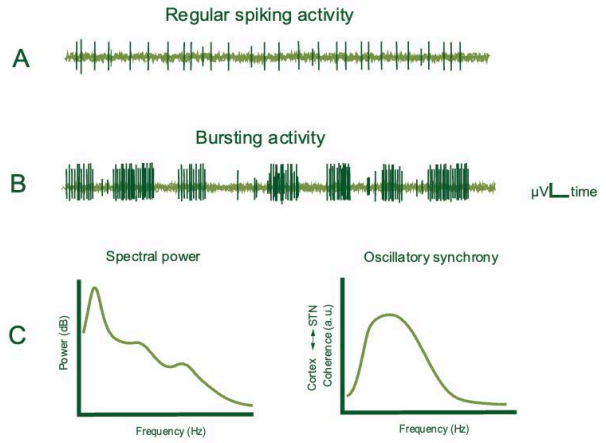

Figure 2. Schematics of different ways to analyze neuronal oscillations. (A) Non-bursting spiking activity of a given neuron and (B) bursting activity across time. A bursty neuron repeatedly spikes, followed by a period of inactivity usually longer than inter-spike intervals before the next burst. In local field potentials, bursting can be defined as a significant increase in the amplitude of an oscillatory signal that lasts more than 100 ms. (C) Signals can be decomposed into the frequency domain to observe how strong they are across rhythms (left) and how different brain regions are synchronized at a given frequency (right). Synchronization is also called coherence or coupling, and it is a measure of connectivity. Adapted from Radcliffe et al (2023).

Methods

All original and review articles considered for this review were first screened on PubMed (https://pubmed.ncbi.nlm.nih.gov/). The terms researched on the database were (Parkinson's disease) AND (beta oscillations) with a filter for publications of the last ten years. Additional studies were found by searching the same terms on Google Scholar (https://scholar.google.com/), with a filter for publications of the last five years. Relevant research referenced by the previously selected articles was also included in this review, as well as classic studies in the field.

Results and discussion

Pathological beta dynamics and its modulation by therapies

Aberrant beta oscillations were first identified in PD patients in the early 2000s and have been observed across the motor cortex and different BG nuclei of the Parkinsonian brain, more predominantly in the STN [18-19]. Studies on beta dynamics have shown that its activity is movement- and task-modulated/related. In healthy monkeys, beta seems to be stronger when there is no ongoing movement (during hold and post-performance periods) [20]. In PD patients, beta power decreases during movement preparation and execution and increases after movement termination [21-23]. Importantly, the latency of subthalamic beta suppression strongly correlates with the reaction time to perform movement, further supporting the idea of the anti-kinetic nature of beta waves [24]. Moreover, artificially driving the STN at the beta band in PD patients leads to the slowness of movement, an effect that is not observed in other frequencies [25-26]. In that sense, exaggerated beta oscillations in the CBGTC loop could delay or even abolish voluntary movement, leading to akinesia and bradykinesia.

Indeed, clinical evidence indicates that beta power is correlated to motor impairment in PD, particularly to bradykinetic symptoms, as assessed

by the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III) [22, 27-28]. Dopamine replacement therapy (levodopa), the gold-standard treatment for PD, reduces beta power while alleviating motor symptoms [27-29], with the degree of beta activity decrease being correlated with symptom alleviation [30-31].

Another PD treatment modality is DBS. To this end, electrodes are chronically implanted in the STN and deliver continuous stimulation at high frequencies (>100 Hz). DBS has proven to be an effective alternative to levodopa, especially for medication-refractory patients. Its efficacy is attributed to the suppression of beta oscillatory activity in the BG [32]. DBS produces similar effects on motor performance as observed with levodopa while also reducing beta power in PD patients [30-33].

Collectively, these findings suggest that beta oscillations may be a pathological hallmark of PD and could serve as a target for developing therapies.

Beta sub-bands

Within the beta range, lower frequencies (8-20Hz) and higher frequencies (20-35Hz) are thought to produce distinct outcomes in PD neuropathology and be linked to different CGBTC pathways. Thus, the beta band is conventionally divided into low beta and high beta.

In MPTP-treated monkeys, increased low beta power is observed in the striatum, STN, and GPe, as well as higher oscillatory synchrony between those nuclei when compared to the healthy condition [32]. In PD patients, low beta power is better correlated to symptom severity and seems to be more sensitive to medication than high beta [29, 34-36].

While low beta is associated with bradykinesia and rigidity in PD [37], subthalamic high beta power has been linked with freezing of gait [38]. Clinical studies have also shown that while medication primarily suppresses low beta power, DBS modulates high beta in the STN and decreases excessive cortical-subthalamic beta coupling [33, 39-40].

Coherence and directionality analysis in the CBGTC network suggest that both sub-bands might be driven by the cortex but through different pathways. While low beta oscillatory activity is associated with the indirect pathway [40], high beta oscillations are thought to represent the signal flow of the hyperdirect pathway [23, 34].

Physiological beta

Neuronal oscillations are not essentially bad. In fact, they may serve various functional roles in different brain networks. For instance, delta oscillations (0.5-3.5 Hz) occur during deep sleep and are associated with learning [41], and gamma waves are involved in sensorimotor integration, attention, and memory formation [42-44].

Beta oscillations are also present in the CBGTC loop of healthy rodents [45], monkeys [32], and humans [46]. The main hypothesis is that beta oscillations originally signal the sensorimotor system to maintain the status quo, promoting the existing state of the system (rest/current motor set) instead of new ones [47].

Beta episodes have been observed in healthy and MPTP-treated monkeys, although their prevalence is higher in Parkinsonian animals [32]. They have also been found in the LFPs of levodopa-treated PD patients, but bursting seems more frequent in the untreated state [48-49]. Burst duration is also different when comparing treated and untreated patients. Shorter bursts are more common in ON levodopa than in the OFF-medication state. While longer bursts are associated with symptom severity, shorter bursts are negatively correlated to motor impairment [50]. These findings suggest that short bursting might have a physiological role, while longer bursts may reflect the pathological features observed in PD [51].

Thus, beta oscillations are part of BG physiology and are thought to have a role in normal movement control. The amplification of beta physiological

levels leading to akinetic outcomes might be explained by changes in the input-output features between BG nuclei, or through the imbalance between the direct and hyper-direct pathways [52].

Optimizing DBS

Conventional DBS systems (cDBS, or open loop DBS) deliver constant high-frequency stimulation to the STN to suppress pathological oscillatory activity. However, this approach can also interfere with physiological neuronal signaling and does not account for the dynamic active state of the patient [53]. A collective ongoing effort is being made to develop a system through which pathological biomarkers are identified to trigger stimulation with real-time adjustments, known as adaptive DBS (aDBS, or closed loop DBS). However, the key physiological and pathological biomarkers to adapt stimulation parameters are still in debate.

Pioneer studies in the field used beta power as a triggering biomarker and observed better therapeutic effects than those obtained with open-loop DBS while reducing its side effects [54-55].

Rhythmic bursting is also a promising target for aDBS. A study on MPTP-treated monkeys revealed that the duration of beta episodes was a more significant feature of Parkinsonian neuronal activity than beta power across the input, intermediate, and output nuclei of the BG [32]. Additionally, computational models designed to predict pathological beta bursts and trigger aDBS were found to be more precise than current aDBS strategies that use beta power as a biomarker [56]. This suggests that burst-driven aDBS could outperform beta power-driven aDBS systems, leading to more promising clinical outcomes.

Conclusions

Beta oscillation features have been extensively linked to PD symptomatology, making them a promising biomarker for invasive electrophysiology therapy. However, considering they are also present in healthy conditions, seem to appear relatively late in the disease progression, and might not be linked to all motor phenotypes observed in PD, their pathological role needs to be further untangled. Future studies should address the temporal dynamics of beta waves in the different BG nuclei in healthy and pathological conditions.

During my PhD journey, I plan to study not only the frequency in which those oscillations occur but also their synchrony and phase relationship within and across BG nuclei during action initiation and execution. Importantly, I want to observe the behavior changes temporally linked to their appearance and their modulation by levodopa intake and DBS.

For now, the above-mentioned literature shows how their involvement in the disease is undeniable, and that studying its dynamics and modulation will lead to a better understanding of the network disruption in PD itself.

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Scientific journalism

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How did it all start?

Before scientific journalism, up to the XVIIth century, new scientific findings were communicated through personal correspondence between scholars, or by publication and distribution of complete books, that summarized several years of work. Scientific journals provided scientists with a way to report their findings and ideas in a relatively fast manner, while maintaining quality by editorial and later peer review. The publication of smaller fragments of research in the shape of a scientific article transformed scientific communication into what it is today [1].

The first regularly issued scientific journal was published in Paris in January 1665, under the title *Le Journal des Sçavans* (*The Journal of the Knowers*) [2]. Denis de Sallo, under the pseudonym *Le Sieur de Hedouville*, founded the journal, with a royal privilege. The preface started with a statement of aim to 'summarize what happens in the intellectual world'. The journal specified its contents as 1) an encyclopedic collection of important recent books, 2) reports on the deaths of famous people, 3) recent discoveries and observations of the natural world, as well as new inventions, and 4) political news in France and abroad. It was intended to be a general newspaper that reported 'everything that happens in Europe and may be important to literate people'. Except for its regular printing, it was not very similar to modern scientific journals – there was no standardized format or peer review process. However, de Sallo fulfilled an editorial-like role, selecting manuscripts, and moderating debates when necessary [3]. Ironically, the journal that revolutionized scientific communication was later ended by the French Revolution in 1792.

In March of the same year 1665, Henry Oldenburg, secretary of the Royal Society in London, published the first issue of *Philosophical Transactions* partly in response to the French *Journal des Sçavans*. He had previously published correspondences from wealthy noblemen, but with little success. Oldenburg

liked the *Le Journal des Sçavans*, and decided to start his own periodically published scientific paper, but in a slightly different way: he concentrated more on natural science advancements than being a general multifaceted scientific newspaper. Hence the name *Philosophical*, which had a much broader meaning of natural science at the time, and *Transactions* which can be translated as 'proceedings' or 'discoveries' in modern English. This journal consisted of the editor's letters, translations from the *Journal des Sçavans*, and manuscripts sent by external authors. Often it published unfinished or planned experiments, if they were sound enough. Oldenburg, challenged by poverty, aimed for the journal to provide financial stability to him and often took a highly visible role as editor, contrasting with modern editorial practices [2].

The two journals were well aware of each other. So much so, that the *Journal des Sçavants* published a warm welcome for the *Transactions,* with some delay – which they explained by a difficulty to find an interpreter who could translate from English to French. Indeed, writing in English at the time was a limiting factor, as Latin, French or German were more widely used across Europe. *Philosophical Transactions* aimed to educate English intellectuals on the continental scientific advancements, rather than the other way around [2].

The advent of peer review – is it a necessary practice?

For over sixty years after their beginning, scientific journals operated and published a great variety of articles, essays, and letters, without a formal peer review procedure. Just imagine: no fussy questions and impossible suggestions from a mean second reviewer, and if the editor selected your manuscript, it might have been even hyped up to sound better!

The editor's liberty to select manuscripts for publication was changed to a more meticulous system of revision, which might have originally evolved from scholarly censorship [4]. In 1731, the Royal Society of Edinburgh published the first issue of *Medical Essays and Observations*, which stated in the preface that

"Memoirs sent by correspondence are distributed according to the subject matter to those members who are most versed in these matters. The report of their identity is not known to the author. Nothing is printed in this review which is not stamped with the mark of utility."

Thus, the pre-printing peer review process was introduced [5]. Other journals followed suit, and The Royal Society of London established a *Committee on Papers*, consisting of five Society members who decided on manuscript acceptance. Likewise, the French *Académie Royale de Médicine* elected four members and selected officers of the society to review submissions, either selecting for publication or returning for modifications after discussing them in general assemblies [5].

This process has evolved over the years but has generally stayed in practice and was institutionalized by the 20th century. One of the main reasons for its persistence is that, in an environment that pushes scientists to publish in higher quantity and soundness, a sort of quality control is necessary to maintain scientific integrity and credibility. A number of studies have assessed the usefulness of peer review, particularly in medical journals. According to them, the majority of authors reported an improvement in quality after peer review [6]. However, other studies emphasize the necessity to improve the process, as it is prone to overlook false or previously published data, as well as the weight of human bias, which has been experimentally detected [7].

Although the process is far from perfect, a way of crosschecking appears to be helpful and even necessary for good research conduct. As every author contributes a brick of knowledge to the grand

theatre of research, it remains a collective responsibility to ensure the quality of those bricks, upon which future technology and therapies are built.

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Insight on Multiple Sclerosis and remyelination therapies

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Reviewed by Dr. Ayal Sooltangos

This section has been created in collaboration with the Maison du Cerveau, an association that brings together all those involved with diseases from the nervous system. Our goal is to increase visibility and to provide information about these pathologies, treatments, and research advancements for the general public.

Thinking about neurodegenerative diseases, people usually think those are disorders coming with age in the majority of the cases. If there is one thing about Multiple Sclerosis (MS) we can say in this area, is that it is certainly not the case. Indeed 80% of diagnoses concern persons between 20 and 40 years old and MS is the first cause of severe non-traumatic disability in young adults. Apart from age, MS is also more common in women with a ratio of 1 man for 3 women.

MS is an auto-immune disease (the immune system attacks the body) that affects the central nervous system (brain and spinal cord). It is often characterized by flare-ups of symptoms interspersed with remitting times where symptoms get better or disappear. The symptoms can also manifest in a more progressive way and slowly worsen over time. Symptoms of MS are extremely heterogeneous from one individual to another, but they can frequently include : fatigue, motor problems with muscle weakness, sensory problems like pain and numbness, visual disorders, balance disorders, urinary problems, sometimes cognitive disorders etc…As the disease progresses, symptoms will worsen and can lead among others to partial or complete paralysis, depression, inappropriate emotional responses and sometimes at very late stages, dementia. There are no current treatments to cure the disease.

How does it work?

Our central nervous system is composed of up to 100 billion neurons, interconnected with each other and allowing us to move, feel, see, breathe, think, have emotions and basically live our lives. In order to do that, all of those neurons have different shapes and characteristics. Each neuron can retrieve information thanks to their dendrites and transform it into an electrical signal to pass the information to the next neuron. This electrical information will be transported along a part of the neuron called the axon that can be very long (the longest axon in the human body is almost 2 meters long), but because the signal is electric, the information will still be delivered quickly (10 to 75 m/s). In order for it to be

delivered even faster, a great deal of neurons are surrounded by a specific membrane that will isolate the axon : a sheath of myelin, allowing the nerve message to speed up (120m/s max).

As it was explained before, MS is an auto-immune disease : the immune system malfunctions and immune cells start to attack and destroy perfectly healthy myelin around the axons. As a result, there will be a perturbation in the transmission of the nerve message that will be the cause of the symptoms. With time, the unprotected axon will be exposed to the extracellular environment and can be degraded : the nerve message cannot pass at all. As immune cells can start attacking anywhere and any kind of neuron in the brain and spinal cord, then it explains the great heterogeneity of symptoms : based on which neurons lose their myelin and on which biological function those neurons were involved in, it will impact different abilities from one patient to another.

About the sclerosis term, it comes from what we see doing an MRI (Magnetic Resonance Imaging), on patients suffering from MS. At places in the brain or spinal cord where myelin and axons have been degraded, the remaining tissue heals, forming sclerotic plaques, which can be detected by the MRI and is specific to the disease.

« Having MS is like being a celebrity. People Always ask how you're doing, and you never have a good answer » Jamie-Lynn Sigler

Cause of MS?

As for many neurodegenerative diseases, the cause of MS is still unknown meaning we don't know what causes the immune system to attack the myelin sheaths. However what researchers have identified through the years is that there exist a bunch of risk factors increasing the likelihood of having the disease. We already talked about age and birth gender. We also have a part of genetics, with certain genes that will constitute a risk factor for the person to develop the disease : it does not mean the person will automatically have MS, but they will be more likely to develop it in their lifetime compared to someone without the genes. But more importantly, there are also environmental factors to consider. Among the best known we find smoking, obesity, already having an auto-immune condition, or even having previously been infected by certain kinds of viruses : like Epstein-Barr responsible for mononucleosis. Interestingly, they also realized that there is a gradient increasing the risk of having MS the more people grow-up away from the equator (whether it's in the north or south direction). This seems to be related with the amount of D vitamin (provided by sun exposure) people have been receiving during their childhood.

Different types of MS and current treatments:

We can classify MS into different forms, depending on the progression of symptoms.

Relapsing-Remitting MS	Primary-progressive MS	Secondary-progressive MS
As already described above, there will be an alternance of relapsing times, where the symptoms will manifest and remitting period with a partial or complete recovery from the relapse. Relapsing times can come up spontaneously or can be triggered by an infection.	Symptoms will slowly and gradually settle in over time, with no remitting times. There can be periods of stability with no progressions of the symptoms.	This one starts as a relapsing-remitting MS, but then at some point will become much more progressive like the primary-progressive one.

Concerning treatments in MS, because of the huge heterogeneity of symptoms depending on the patients, the choice of the course of treatment will be very patient depending. Treatments will allow to delay the disease progression and alleviate the symptoms, but none of them are currently curative. As it is an auto-immune disease, immunosuppressant and immunomodulatory medication are widely used as ongoing treatment to prevent more myelin degradation, but this comes with many side effects due to the shutdown of the immune system. More recently immune reconstitution therapies have started to emerge, with the aim to eliminate the pathogenic immune repertoire from the body but keeping the healthy cells. In order to alleviate the different symptoms, a lot of MS non-specific treatments are given, each of them targeting one of the symptoms patients may have (those are treatments we can find in many other pathologies).

Research advances : highlight on remyelination in MS

Many new treatments and therapies are currently being studied in research laboratories and hospitals, some of them with really promising outcomes. One of them is the concept of remyelination in the nervous system of MS patients. After a loss of myelin, it has been shown that in some MS patients, cases of remyelination can occur on their own. Only it is in negligible proportion to have any impact. Remyelination happens after a loss of myelin when cells responsible for the production of myelin, oligodendrocytes, are newly created. However it is not a process large and effective enough to compensate for the myelin loss (not enough new myelin is created and it is of poorer quality compared to the previous one). In order to create new oligodendrocytes, undifferentiated cells are needed, meaning, cells that have not yet specialized as oligodendrocytes (they do not have a job yet). Those cells receive different kinds of signals: some pro-differentiation and some anti-differentiation. More pro-differentiation signals and less anti-differentiation signals can lead to the differentiation of the cell. That is exactly what is currently tested in pre-clinical research and clinical trials : molecules that are able to promote stem cell differentiation into oligodendrocytes to reform the myelin after its destruction by the immune system. Many molecules are currently tested, we can mention Clemastine, an anti-histamine that can promote differentiation into oligodendrocytes and therefore increase remyelination. There is also Opicinimab, a Lingo-1 antagonist (Lingo-1 being a negative regulator for oligodendrocyte differentiation) that can likewise promote remyelination. However, the remyelination process only works on intact axons that have not degenerated yet, therefore this kind of treatment would only be effective at the onset of illness with limited damages. Hopefully, many other kinds of therapies are still tested to help patients with different forms and progression of the disease, as well as future patients that may develop multiple sclerosis in the future.

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Women's Voices: inspiring the neuroscientist community

Anushka Nair

Sara Carracedo[1]
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Women's Voices is an interview section created in partnership with the Neurocampus Parity and Inclusion Committee (NeuroPIC), a local group committed to promoting equality and organizing actions to close the gap between women and men in academia. The goal of this section is to increase the visibility of early career female researchers at the Bordeaux Neurocampus of the University of Bordeaux. We interview researchers about their scientific contributions, insights and opinions about equity, diversity, and gender bias in academia. Through these interviews, we aim not only to highlight their achievements but also to serve as inspiration for our scientific community and other female scientists.

Together, we will bridge the gap!

This month in Women's Voices, we interview **Anushka Nair**, a PhD student originally from India working at the IINS. Anushka began her academic path in Mumbai, where she studied Biotechnology. After, she did the Neurasmus Master's in Neurosciences in The Netherlands (1st year) and Bordeaux (2nd year). After completing her Master's internship at the Bordeaux Neurocampus, she stayed in Bordeaux for pursing her PhD, where she works on synthetic nanobodies. In this interview, she shares her academic journey and opinions about some challenges international students can face when working in Europe.

Sara Carracedo: Could you start by sharing a bit about your academic journey?

Anushka Nair: My name is Anushka Nair and I am in the third year of my PhD at the IINS under the supervision of Dr. Jonathan Elegheert. I am originally from India and I completed my formative years of education there. I further pursued an engineering Bachelors in Biotechnology in Mumbai and then obtained a fellowship for the Neurasmus program which allowed me to do the 1st year of my Master's in Amsterdam and the 2nd year in Bordeaux.

From early 2021, I started my PhD project titled "Targeting synaptic proteins and receptors with synthetic Nanobodies". I am currently in the process of continuing the PhD with a 1-year extension to see the project to fruition.

Sara Carracedo: Could you tell us more about your research and achievement obtained during your PhD?

Anushka Nair: My PhD project aims to develop molecular tools that will be used to determine iGluR composition and trafficking at the synapse. For this, I am establishing an in vitro synthetic Nanobody (sybody) discovery workflow to discover high-affinity subunit-specific binders.

We start with three structurally distinct sybody libraries, each having an initial diversity of 10^12-10^13 unique sequences, which are screened for binders against a target protein by performing a combination of various selection techniques such as ribosome display, phage display and yeast surface display. After the selections, we typically converge upon 10-20 sybodies against the target which are further biophysically, biochemically and structurally characterized. These synthetic binders will then be used to study iGluRs using super resolution microscopy.

During the PhD, I have had the opportunity to present my work at reputed conferences and meet experts in the field from across the globe. I have also had the chance to be part of Women in Science committees, which has given me a platform to share my experiences with other young researchers. Additionally, my experience here has given me the chance to help youth in India who are enthusiastic about the field of neuroscience.

Sara Carracedo: Can you describe the state of neuroscience research and opportunities in your home country (India)? How does it compare to what you have experienced in Europe?

Anushka Nair: Neuroscience research in India has been expanding steadily and several leading institutions in the country have been focusing on different streams of research such as cognitive neuroscience, computational neuroscience, and clinical neuroscience. Different government organizations, including the Department of Biotechnology (DBT), the Indian Council of Medical Research (ICMR), and the Council of Scientific and Industrial Research (CSIR), are providing substantial funding and various platforms for neuroscience research.

In comparison to Europe, there is still a need for more infrastructure across universities and for talented individuals to pursue research in the country itself.

Sara Carracedo: What challenges did you face in obtaining a visa to study or conduct research in Europe? How did these challenges impact your academic and research plans?

Anushka Nair: Being a non-EU student, the visa application process was truly a testing period. The documentation required and the necessary approvals took a long time, and this was very stressful since one is in a constant state of uncertainty, until such time that you receive the green signal from respective authorities. Additionally, the process of applying for a research permit for me was during the COVID period, and this complicated matters since I could not travel to India to complete the application and, instead, I had to get everything done in Europe itself. This affected my work in terms of time and energy, since I was required to travel between Belgium, Netherlands and France for the permit and had to be prepared for a situation where my research would be put on hold if I had to travel back to India under immediate circumstances.

Sara Carracedo: In your opinion, how does the difficulty in obtaining visas impact the global exchange of knowledge and ideas within the neuroscience community? What measures could be implemented to make it easier for international researchers to work in Europe?

Anushka Nair: I understand the legalities and restrictions that come with visa procedures, however, in my opinion, the time consuming nature of these processes does negatively impact the exchange of knowledge and ideas. It restricts mobility between different labs and thus limits access to resources. Also, time sensitive experiments can be affected, which leads to delayed results and overall lower research productivity.

One of the critical measures I think could help the community would be to have some flexibility in terms of permit or visa deadlines. Additionally, fast tracked methods to expedite approvals would really help, especially for cases where the researcher just needs an extension of a few months or a year to complete their work.

Sara Carracedo: What advice would you give to other early career women from abroad who wish to pursue a PhD in Europe?

Anushka Nair: Having been in Europe for over 5 years now, I would first highly recommend female researchers to come to Europe and experience the research environment here. I believe the work culture and ethics are very enriching here. The only advice I would give would be to be aware of how the system works and what documentation is required throughout your stay. Having said that, plan your PhD in such a way that you take into account hiccups related to visa processes, so that when such issues arise, your work is not drastically affected.

NeuroPath: exploring careers beyond academia

Graziano Pinna, scientific advisor and associate professor

Ludovica Congiu[1]
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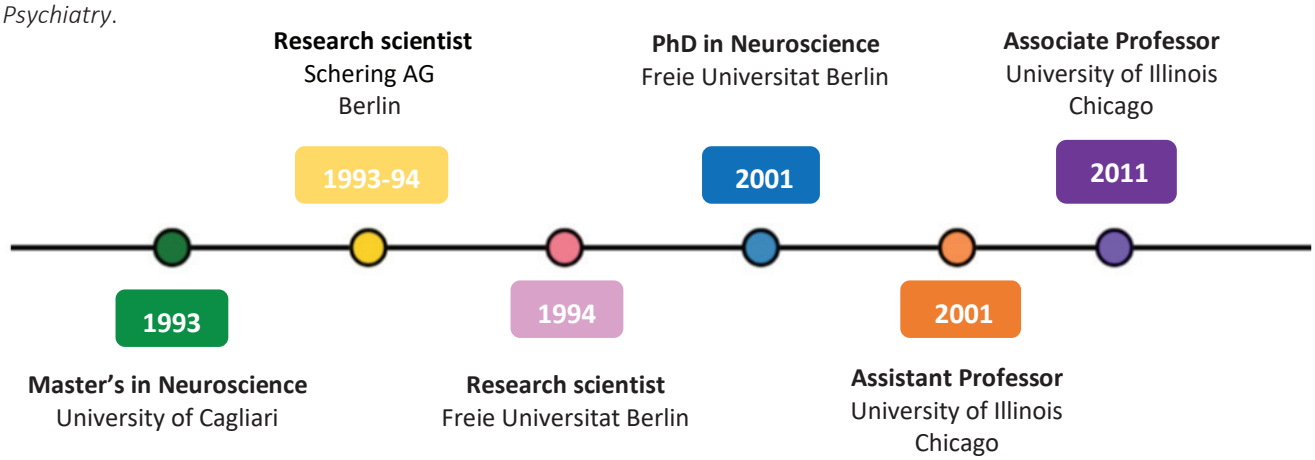
The world of science offers many exciting paths, and academia is just one of them. Each year, both the public and private sectors actively seek PhD graduates to fill diverse roles. However, many of them may seem unfamiliar to most of us. At Brainstorm, we want to help you explore career options that align with your interests, and aspirations.

That's why we created NeuroPath: a section dedicated to highlight scientific related careers outside academia. We reached out to professionals, who like us, have earned a PhD in neurosciences, most of them from the Neurocampus, but chose to apply their expertise in different fields. Through their stories, they share insights into their career journeys and practical information regarding their current positions.

Science is a lifelong pursuit, but the path you take is yours to choose.

Follow the one that excited you the most!

This month in *Neuropath*, we spotlight **Graziano Pinna**, an Associate Professor of Psychiatry at the University of Illinois at Chicago (UIC). Dr. Pinna is renowned for his work on the neurobiology of PTSD. Beyond the lab, he strives to translate his research into real-world treatments and to raise awareness about PTSD by collaborating with top institutions like Johns Hopkins, Harvard, and Cornell. His dedication extends to mentoring young scientists and engaging with mental health organizations to promote education and support for trauma survivors. Dr. Pinna also serves as Deputy Editor for *Stress & Health* and on the editorial boards of *Neuropharmacology* and *Progress in Neuropsychopharmacology & Biological Psychiatry*.



Are you interested in combining public research while collaborating with industry? Then this section is for you!

Scientific advisor and associate professor

Graziano Pinna

I collaborate with biotech companies as an advisory board member helping translate neurobiological discoveries into therapeutic strategies

Main tasks

- Project planning, funds acquisition, study design
- Supervision of data analyses
- Supervision of junior faculty, post-docs, MD, graduate students
- Paper writings

Requirements

PhD in neuroscience or related disciplines

Working conditions

Work environment: Excellent

Pressure level: very high

Work-life balance: to improve

Salary: is quite good within the USA standards

Do you have further questions?

Contact Dr. Pinna at gpinna@uic.edu

What is your role outside academia?

Outside academia, I collaborate with biotech and pharma companies as a scientific advisor, helping translate neurobiological discoveries into therapeutic strategies, especially in neuropsychiatry and women's mental health. This role allows me to bridge the gap between basic science and clinical application.

Why did you choose this professional

My curiosity about the brain and behavior led me to neuroscience, but what really drove me was the desire to make a difference in how we understand and treat mental illness. The stigma surrounding psychiatric disorders, especially PTSD, inspired me to focus on translational research—work that can go from bench to bedside and, hopefully, impact lives.

What's a matching profile?

A good fit for this path is someone who thrives in interdisciplinary environments, is deeply curious, and is motivated by making an impact in the field. There is still a lot of room for making an impact in women mental health owing the fact that the field has been notoriously left behind. You need resilience, a collaborative spirit, a lot of determination to succeed, and a passion for connecting dots. Being open to crossing academic boundaries and engaging with industry, policy, or public health is key. Altogether, to succeed in this field in addition to all these qualities, you need to devote a lot of time, this is not a 9-to-5 job.

Why did you choose the US over Europe to build your career?

The United States offered greater flexibility and more opportunities for translational research and funding in psychiatry. The system values bold ideas and high-risk projects, which aligned well with my vision of connecting neurobiology to treatment development. Moreover, my expertise in using the state-of-the-art gas chromatography-mass spectrometry (GC-MS) to quantify and study neurosteroids positioned me competitively, and I was offered a faculty position immediately after completing my PhD—effectively skipping the traditional postdoctoral route. That said, I continue to value my European roots and maintain strong ties with Italy through collaborations, scientific interactions, and mentoring.

Main differences between the US and Europe in terms of job opportunities?

The US system generally supports early independence, offers greater access to federal and private funding, and encourages collaboration between academia and industry. In Europe, the path can be more rigid, with fewer funding sources and longer timelines for career advancement. That said, European institutions often offer stronger foundational training and a more balanced approach to research and life.

How did you build the relationship between your academic role and companies?

It started organically—through scientific meetings, collaborative research, and shared interests in translating discoveries. Publishing in high-impact journals and speaking at conferences helped build visibility. From there, discussions with companies evolved into advisory roles and research partnerships. A mutual interest in developing biomarkers and novel therapeutics made those collaborations a natural fit. The approval of allopregnanolone as Zulresso (IV infusions) and as Zurzuvae (oral administration) by the FDA helped stimulate the interaction between academia and industry for many of us who dedicated their career to study neurosteroids in mental health.

Do you have some advice for PhDs interested in this path?

Yes! Don’t silo yourself. Explore beyond your dissertation. Attend conferences outside your niche, connect with professionals in industry, and seek mentors who bridge sectors. Learn how to communicate your science clearly, even to non-experts. Most importantly, be open to evolution. Your career doesn’t have to fit into one box, it can be a hybrid of passions, roles, and impact, and… hard work and determination to succeed!

Back to the stem

Interview with Anna Falk

Juan Garcia-Ruiz[1]
[1]Glia-neuron interactions team, Neurocentre Magendie, University of Bordeaux

What's neuronhub? It is an outreach website hosting interviews with researchers from all corners of the planet about their work in the field of neuroscience. The idea is that you get something from people who have a long career in science, that you learn something new and cool, and above all that you don't lose track of the latest discoveries in neuroscience that are being made in other parts of the world.

Keep up to date with neuroscience by subscribing to the newsletter. Compensate for the useless spam you receive with high quality material! Scan the QR code here:

Did you encounter a problem scanning the QR code? Join the newsletter directly in eepurl.com/gUHG8T

I am sure you know who Benjamin Button is. But do you know Shinya Yamanaka? Unlike Benjamin Button, Yamanaka is not the protagonist of a movie where he defies ageing and grows younger from old age to childhood. He is a real, flesh-and-blood scientist. A scientist that has won more awards than I could list here without making you close the tab. But to make my point, I'll mention just one: the 2012 Nobel Prize in Physiology or Medicine in 2012 (which he shared with John Bertrand Gurdon).

What is your point, Juan? What does Benjamin Button have to do with Professor Yamanaka and his Nobel Prize? — You mentally ask. Yamanaka (along with Gurdon and the many researchers that worked under their guidance or collaborated with them) has come closer than anyone to making the curious case of the case of Benjamin Button a reality. They challenged one of the most fundamentals laws of biology: aging. They showed with their research that mature cells could be reprogrammed into stem cells.

But how this whole rejuvenating mature cells actually work? What the researchers I mentioned earlier discovered in 2006 was that introducing a specific set of genes (known today as Yamanaka factors) into differentiated cells could reprogram them back into a pluripotent state. These genes encode transcription factors that play key roles in gene stability, cell self-renewal, and survival.

Their discovery holds great promise for reversing aging by regenerating damaged tissues, replenishing lost cells, and even resetting cellular age. Crazy, I know. But don't get too excited about the fountain of youth: we are not there yet. Reprogramming cells comes with risks. As previously said, some of the Yamanaka factors play roles in cell survival, so they can potentially increase the risk of tumor formation. And that's not even considering the unpredictable effects they might have on complex tissues. So, while real-world applications for widespread age reversal remain speculative, this is a big revolution in the field of regenerative medicine. And I have interviewed the perfect person to tell you more about it.

Anna Falk is a molecular biologist specialized in neural stem cells and adult neurogenesis. She did her undergraduate in molecular biology at Umeå University and then her PhD at Karolinska Institutet during the early days of human pluripotent cells and also of adult neurogenesis. After that, she did her postdoc in Cambridge University, working with cell reprogramming. Then she went back to Karolinska to start her new lab in 2012. In parallel, she founded a built-up iPS Core facility (https://ipscore.se), a kind of cell vending machine. Lately, she was recruited in Lund University.

Juan García Ruiz: How would you explain in a simple way what an induced pluripotent cell is?

Anna Falk: It's a cell that represents a human embryo very early in development, so it can become any kind of cell later on, and that's why it's called pluripotent. This pluripotent cell can be induced, for instance, from a somatic cell. Usually skin cells from a little skin biopsy or blood cells from a blood sample are used. The idea is that you can rejuvenate the cell, making them useful for many other functions.

JGR: How far back does your interest in stem cells go?

AF: During my undergraduate, I chose a molecular biology program because I was interested mainly in genes. During the undergraduate, I assisted to a research seminar led by Jonas Frisén, who ended up being my PhD supervisor later. This seminar was about stem cells and it was very inspiring to me, so I think my interest in the field started to emerge at that moment.

JGR: How far in the differentiation can we go from an induced pluripotent cell? Let's say we obtain neurons from pluripotent stem cells. Can we also manipulate the type of neuron we get?

AF: First, from a somatic stem cell, you get the induced pluripotent cell by using the Yamanaka factors (editor's note: explained in the introduction). Then there are two different ways of obtaining the cell that you want. Either you add the transcription factors to program the cell in a way that it becomes, for instance, a dopaminergic cell, or you mimic the environment that dopaminergic cells should be in during development, so that the cell is in presence of the necessary elements to become this kind of cell. So yes, it is possible to define cellular identity to a certain extent.

JGR: What's the idea behind stem cell therapy? Can you give a concrete example of the process?

AF: Let's say you need cartilage cells in your knee because you are injured. We take a tiny skin biopsy, and then we grow these cells and use the Yamanaka factors to obtain stem cells. At this point the cells are immortal so we can grow them forever and freeze them down to keep them. So at this point we have your induced pluripotent cells. The next step would be to differentiate them into chondrocytes, which are the cells of cartilage tissue. All of this need to be done in very clean conditions, and these are the steps that need to be done in the special stem

cell cores. Once you have the chondrocytes you can freeze them and put them in vials and send them to wherever they are needed, and they are ready to be injected into your knee. That's the future of stem cell therapy.

JGR: And what's the present?

AF: I can give you the example of a patient in the US that has been cured from type I diabetes. Douglas Melton is big in making pancreatic beta cells. So this patient doesn't have to take anymore insulin. So it's already occurring in some places, and there are some trials going on in Europe. The whole field is a big on a balance. We still need to get good human results to be able to continue to get money into this.

JGR: What are the limits of these kinds of strategy of obtaining differentiated cells? Let's take neurons as an example.

AF: Some neurons have not been of interest for the scientific society, so we might not be able to get them. I took dopamine neuron as an example because they have been of interest for a long time because of its relationship with Parkinson's disease. Another problem is the ageing. The pluripotent cells that we use are like an embryo cell that is just a few days old, so they are very young neurons. If you compare them with mature neurons from an adult human, for instance, you can see that they are not exactly the same partly because of this. And then there is the problem of the physiological environment. Sometimes neurons need to be in contact with other cells, especially with astrocytes, to mature and to do its proper functions. That is why we work a lot with 3D structures like brain organoids. It's important to consider having more than just one layer of neurons because that's not reality. However, for some types of therapies the strategy is to have just one type of neuron, so actually this aspect really depends on the final goal of the cells.

JGR: What are the main advantages of doing research with induced pluripotent cells compared to other approaches to deal with a biological question?

AF: It's possible to create cellular models in the lab, especially similar to human tissue that would not be accessible otherwise. We can model neuropsychiatric and neurodevelopmental disorder and mimic these person's brains to study them. We can mimic for instance how the brain of a person with a certain disease develops, and then we compare to a healthy brain model and see if there's something in the course of development that was not right. That's one of the advantages. But you can also create a great amount of cells for therapy, for instance you can develop unlimited dopamine neurons for cell replacement, or insulin-producing cells for diabetes patients.

JGR: What is neurogenesis and how do you study with induced pluripotent cells?

AF: Neurogenesis is the process of creating neurons. There is neurogenesis during development, when the pluripotent cells have the potential to become any cell, but they undergo different steps that make them differentiate into neurons. So the first step is the production of the neural progenitor, the neural stem cell, and then there is a big expansion of these neural progenitors because those are the ones that are going to build up the whole brain in terms of neurons. It is very important that this whole process goes right. But sometimes there are some failures. The causes of the failures are sometimes genetic and sometimes environmental, like toxins or stress. So how do we study all this? You know for example that neurons should migrate into the right of the cortex. Then you can take neurons from a patient in which you observe that the neurons are not migrating correctly. So then you can do all kind of experiments to see what might be causing this problem. Or you can observe that some neurons are not maturing as they should, and you can then study their signaling with electrophysiology approaches. Sometimes what you observe is a difference in the kinetics: some neurons are differentiating faster or slower when compared to the cells of a healthy control. Or yet you can see that the fate choice of the neural stem cell of a patient is making less neurons than a healthy control, and you can then study why this is occurring.

JGR: What are the main discoveries made in your team?

AF: We have found that in early stages of neurogenesis, when the neural stem cells are supposed to differentiate, you can already detect some phenotypes that were believed to appear much later in development. In other words, we have found that it's not that the neurons of neurodevelopmental disorder patients developed normally and started going wrong later, but actually they were already not functioning as they should early in their development. This is also the case for mental disorders such as schizophrenia: you can have be diagnosed at 28 years old, but it doesn't mean that the problem started there. Maybe the development seemed functional because it didn't reach a threshold to be noticeable, and they almost did it as a healthy control but not exactly like that, and then the issues continued developing later on until the first visible manifestations started to emerge.

JGR: What are the black boxes in this field of study?

AF: We don't know perfectly how to do iPS cultures in a way that the cells are very standardized. It's still a discussion in the field and because certain iPS cells are better suited to develop a certain kind of cell than other iPS cells. And yet, both iPS come from healthy people with a functional brain, so it's very strange. So I would say the black box lays there, in the complete standardization of the iPS cultures with no epigenetic traces.

JGR: How do you envision the evolution of the field from now to 2050?

AF: I think we will use stem cells for curing diseases where cells have died or have been injured. We are definitely going to do replacement therapies in human with cells coming from iPS cells.

JGR: What is the most science-fiction experiment that you would do if you could?

AF: Well, the organoids are like mini brains floating around a dish. But in these conditions they lack vessels, they lack immune system, etc. So the science fiction experiment would be to really create mini brains but with all the other tissues that are actually in the brain. But that comes with ethical considerations. What about if these mini brains start thinking?

JGR: Do you have a message you would like to share with the readers?

AF: Go for what is fun! Don't think too much about what other people are doing, just follow the joy.

For more interviews, visit www.neuronhub.org

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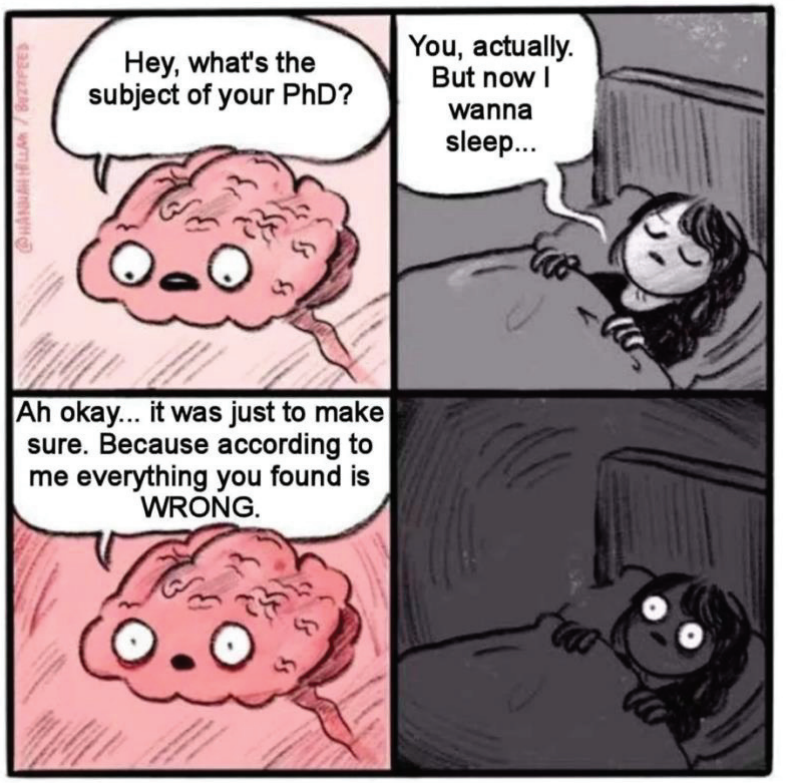

Simon Lecomte, 4th year PhD student at the IINS

Formations

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This is a Zoom online training, happening on 6th May 2025.

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This is a 3-days workshop from 26th May to 28th May 2025.

Editorial board

Aude Verboven

Aude, directly coming from Bordeaux, is a PhD student at the IMN. She previously graduated from the MultiPublic track of Bordeaux Neurosciences Master. She is currently studying the dopaminergic afferences to pain modulating nuclei in the context of Parkinson's disease.

Sara Carracedo

Born in Spain, Sara is a Postdoctoral student at the IMN. She holds a Veterinary Medicine Bachelor's degree from the University of Santiago de Compostela, the NeuroBIM Master's degree and a PhD in neurosciences from the University of Bordeaux. Her Postdoc is focused on understanding the neuroimmune role of P2X4 receptor in Amyotrophic lateral sclerosis.

Toshiko Sekijima

Toshiko, originally from New Zealand, is currently PhD student at the Nutrition et Neurobiologie Intégrative (Nutrineuro). She holds a bachelor's in Biology from the University of Hawaii and a master's in agro-biomedical Science from the University of Tsukuba, Japan. She is also passionate by scientific illustration!

Juan Garcia-Ruiz

With two Bachelor's degree, in Psychology and Biochemistry, and the NeuroBIM Master's degree from the University of Bordeaux, Juan is pursuing a PhD focused on the role of lactate in basal synaptic transmission. Although he speaks near-perfect French, Juan comes from Huelva, Spain. He is also the co-founder of neuronhub (www.neuronhub.org).

Daniele Stajano

Daniele Stajano was born in Naples (Italy). He has a Bachelor's degree in Biology and a Master's degree in Neurobiology. After his Ph.D. in neurosciences at the ZMNH of Hamburg (Germany), he joined as postdoctoral student the IINS. He is currently interested in molecular mechanisms orchestrating brain maturation in neurodevelopmental disorders such as the autistic spectrum disorder.

Ludovica Congiu

Hailing from Sardinia (Italy), Ludovica obtained a master's degree in Neuropsychobiology at the University of Cagliari and pursued a Ph.D. in neuroscience at the Universitätsklinikum Hamburg-Eppendorf (UKE) in Hamburg. Currently, she is a Postdoctoral student at the IMN, where she is investigating the role of P2X4 receptors in ALS and anxiety disorders.

Simon Lecomte

Simon is originally from Lyon, France. He did his Bachelor's of Psychology from Strasbourg, after which he did the NeroBIM master's degree from the University of Bordeaux. He is a PhD student in the IINS where he is studying how the Fragile X Syndrome impacts the presynaptic mechanisms at the DG-CA3 synapses.

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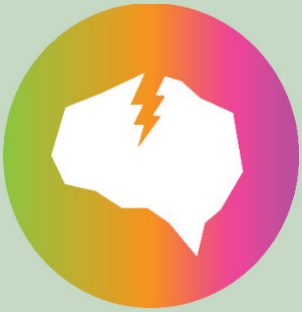

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