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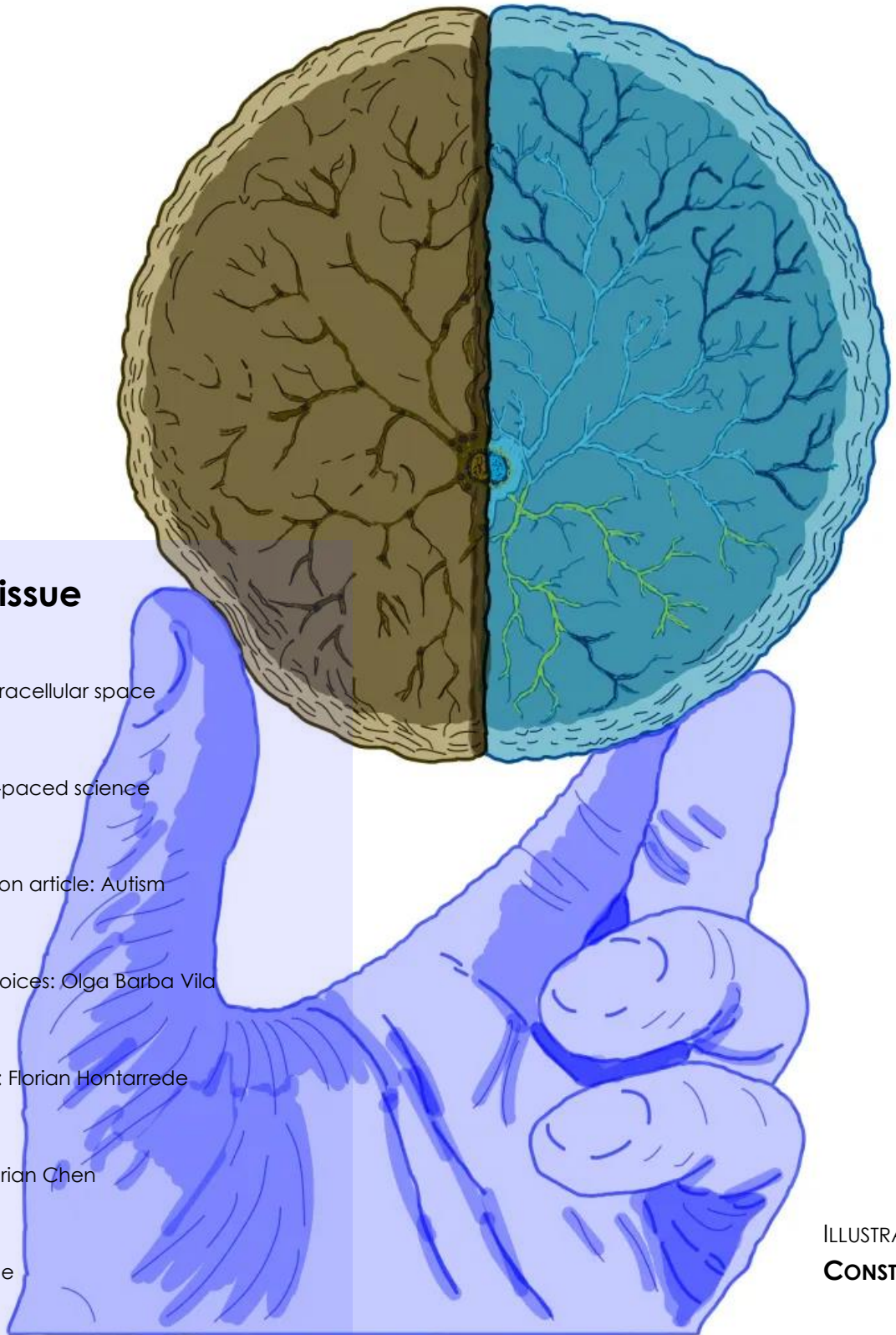

In this issue

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VALUES

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All authors take responsibility for the content of their publication.

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TABLE OF CONTENTS

Extracellular space remodeling in synucleinopathies: insights from nanoscale diffusion studies

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Anna comes from Conegliano, Italy, and holds a Master's degree in Chemical and Pharmaceutical Technologies from the University of Ferrara. She is currently a PhD student at the IMN, where she studies changes in the brain's extracellular space in the context of neurodegenerative diseases.

Abstract

The brain extracellular space (ECS) is a dynamic compartment essential for molecular diffusion, signalling, and homeostasis. Recent studies using models of synucleinopathy reveal that alpha-synuclein pathology, both extracellular and intracellular, can remodel the ECS, leading to increased volume and enhanced nanoscale diffusion. These alterations arise through mechanisms such as extracellular matrix (ECM) degradation and changes in cellular morphology, particularly involving hyaluronan and glial reactivity. ECS remodelling may influence the spread of pathogenic proteins and affect intercellular communication. By integrating advanced imaging techniques, researchers are uncovering the ECS's active role in brain physiology and pathology, highlighting it as a potential target for future therapeutic strategies.

Keywords

Brain extracellular space, diffusion, alpha-synuclein, synucleinopathy, extracellular matrix remodeling

Abbreviations

ECS – extracellular space

ECM – extracellular matrix

HA – hyaluronan

α-syn – α-synuclein

PFFs – pre-formed fibrils

Introduction

The brain extracellular space (ECS) constitutes the fluid-filled interstitial compartment between neurons, astrocytes, and other glial cells. Occupying approximately 15–20% of total brain volume under physiological conditions, the ECS forms a highly dynamic and heterogeneous environment that facilitates the diffusion of ions, neurotransmitters, metabolites, and signalling molecules (1). This compartment is not merely a passive conduit but actively participates in maintaining ionic balance, supporting volume transmission, and enabling the clearance of waste products through glymphatic and perivascular pathways.

Key physical properties of the ECS—including volume fraction, geometry, and tortuosity—directly influence diffusion kinetics and are tightly regulated under normal conditions (1, 2). Subtle alterations in these parameters can significantly impact neuronal excitability, synaptic efficacy, and the distribution of bioactive molecules (18). Importantly, the ECS serves as a key determinant in the movement and accumulation of pathogenic proteins, such as alpha-synuclein, amyloid-β, and tau, which are central to the pathophysiology of major neurodegenerative disorders (4).

In diseases like Parkinson's disease and related synucleinopathies, the progressive aggregation of alpha-synuclein is traditionally viewed as a primarily intracellular phenomenon. However, recent studies suggest that alpha-synuclein can also influence the extracellular environment, either by being released into the ECS or by indirectly modifying its structure and function through neuroinflammatory and glial-mediated mechanisms (3, 8, 21). These changes may alter the ECS's ability to support molecular trafficking and waste clearance, thereby contributing to disease propagation and severity (9).

Despite its critical role in brain homeostasis, the ECS has historically received less attention than intracellular organelles in the context of neurodegeneration, partly due to the technical challenges of studying it *in vivo* at appropriate spatial and temporal resolutions. Advancements in high-resolution imaging, such as super-resolution microscopy, cryofixation electron microscopy, and single-particle tracking, have recently allowed researchers to probe ECS structure and diffusion at the nanoscale (13, 14).

The ECS is shaped by both the extracellular matrix (ECM), composed of key structural molecules including hyaluronan, proteoglycans, and glycoproteins (the most abundant and essential components) composed of hyaluronan, proteoglycans, and glycoproteins, and by the morphology and activity of surrounding cells (11, 22) (Fig.1). Reactive gliosis, neuronal shrinkage, and ECM degradation are all factors that can dynamically alter ECS geometry during disease (10, 12, 20). Investigating how neurodegenerative processes remodel the ECS is therefore essential for understanding brain dysfunction, opening novel therapeutic avenues aimed at preserving or restoring the integrity of the extracellular microenvironment (17).

The purpose of this review is to explore the most recent insights into the structure and function of the ECS, and to highlight its emerging role in the pathogenesis and progression of neurodegenerative diseases, especially synucleinopathies.

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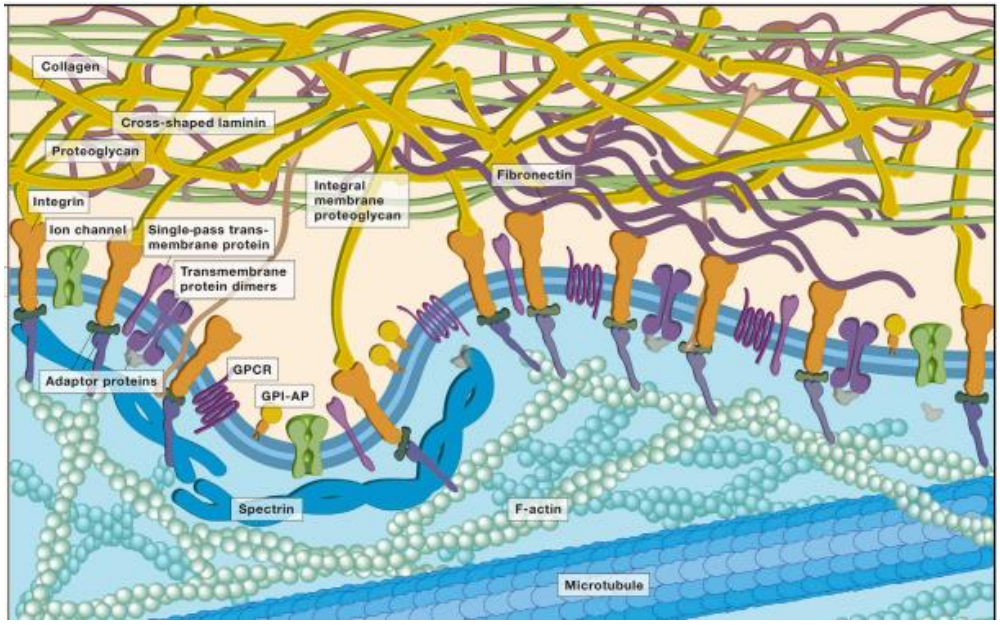

Fig.1. The lateral organization and mobility of plasma membrane components. Adapted from Jacobson et., al 2019.

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 (extracellular space of the brain) AND (extracellular matrix) AND (single particle tracking) AND (single-walled carbon nanotubes) AND (quantum dots). Additional studies were found by searching the same terms on Google Scholar (https://scholar.google.com/).

Soria et al. used cryofixation electron microscopy and live single-particle tracking with single-walled carbon nanotubes to investigate ECS structure and diffusion in the cortex of α-synuclein transgenic mice and mice injected with α-syn aggregates. They also performed enzymatic degradation of hyaluronan and pharmacological ECM modulation to assess HA's role in ECS remodeling and diffusivity.

Estaun-Panzano et al. applied near-infrared single-particle tracking and super-resolution trajectory analysis in acute striatal slices from mice injected with α-syn preformed fibrils. They assessed ECS diffusivity and geometry under pathological versus control conditions, distinguishing ECS alterations caused by intracellular α-syn assemblies in the absence of neurodegeneration.

Results and discussion

Alpha-synuclein-driven matrix remodeling alters ECS diffusion.

Soria et al. (2020) provided compelling evidence that α-synuclein-induced neurodegeneration leads to an enlargement of the ECS, accompanied by a significant increase in the nanoscale diffusion of molecules within this compartment (5). This enlargement was linked to degradation of the hyaluronan matrix, a major structural component of the ECM, particularly in brain regions adjacent to reactive microglia (19). Hyaluronan plays a critical role as both a diffusional barrier and a tissue organiser, maintaining ECS integrity and regulating the movement of solutes. Experimental enzymatic depletion of hyaluronan *in vivo* further

increased ECS diffusivity, confirming its function in restricting molecular mobility and shaping ECS geometry (5). These findings overturn prior assumptions that synucleinopathy leads to ECS constriction, instead indicating that ECM remodelling facilitates enhanced molecular diffusion. This may influence how toxic proteins and signalling molecules spread or are cleared, underscoring the ECM's critical role in disease progression and intercellular communication (9).

Intracellular aggregates increase ECS diffusion in the striatum.

Estaun-Panzano et al. (2024) explored ECS alterations in a mouse model of α-synuclein pathology induced by striatal injection of α-synuclein pre-formed fibrils (PFFs). This model generates intracellular α-synuclein inclusions without extensive neurodegeneration or extracellular aggregation (3). Remarkably, the authors observed a significant increase in ECS nanoscale diffusion compared to controls, demonstrating that intracellular aggregates alone can modulate the ECS environment. While the exact mechanisms remain unclear, potential contributors include subtle changes in neuronal or glial morphology and function, all of which can influence ECS volume and tortuosity (19, 21). These results emphasize that intracellular pathology exerts a profound impact on ECS properties, independent of gross tissue damage, suggesting that early ECS remodelling may precede and contribute to later neurodegenerative processes.

Extracellular space: a site of convergent ECS enlargement and increased diffusion

Together, these studies reveal that different pathological triggers—extracellular matrix remodelling and intracellular α-synuclein aggregation (7)—converge on a common outcome: increased ECS volume and enhanced diffusion. The study made by Soria et al. reveals that alpha-synuclein pathology transforms the brain's extracellular microenvironment by expanding and altering diffusion within the ECS, primarily through HA degradation and microglia activation, while Estaun-Panzano et al. provides compelling evidence that intracellular α-synuclein assemblies alone can alter ECS diffusion dynamics in the striatum, without neurodegeneration, highlighting a non-cell-death-dependent mechanism by which α-syn pathology may spread and influence disease progression. This challenges the classical view of ECS constriction in neurodegeneration and instead highlights a more nuanced and dynamic remodelling process (10). The ECS changes appear to be context-dependent, potentially reflecting disease stage, brain region, and specific pathological stimuli. Understanding how these alterations interrelate and evolve through time will be essential to decipher their role in synucleinopathies.

Functional implications of ECS alterations

The observed increased diffusion within the ECS carries significant functional implications. Enhanced molecular mobility may facilitate clearance of toxic proteins and metabolites through extracellular routes or glymphatic pathways, potentially counteracting disease progression (18). Conversely, increased ECS volume and diffusion could also accelerate the extracellular spread of pathogenic α-synuclein species, promoting disease propagation across brain regions (3, 16). Moreover, ECS enlargement may affect neurotransmitter spillover and volume transmission, altering synaptic and extrasynaptic signalling dynamics and influencing neural network excitability. Changes in ECS structure could further modify local ionic microenvironments and inflammatory signalling, contributing to neuronal dysfunction and vulnerability. These multifaceted effects highlight ECS remodelling as both a potential compensatory mechanism and a driver of pathology.

Cellular and ECM contributions to ECS remodelling

ECS geometry results from the interplay between ECM components and the spatial arrangement of cellular elements, including neurons, astrocytes, and microglia (11, 20). In synucleinopathies, reactive gliosis and altered neuronal morphology likely contribute to ECS remodelling (15). Soria et al. demonstrated that hyaluronan degradation directly increases ECS diffusivity, emphasising the ECM's structural role. In contrast, Estaun-Panzano et al. showed that intracellular α-synuclein aggregates indirectly increase ECS diffusion, suggesting additional cellular mechanisms are involved, potentially including cytoskeletal remodelling, altered vesicular trafficking, or astrocytic volume changes (18). Further research is required to elucidate these mechanisms and determine how intracellular pathology communicates with the extracellular environment to drive ECS changes.

Future perspectives for ECS-targeted interventions

The insights from these studies highlight the ECS as a promising therapeutic target in synucleinopathies. Soria et al. found that enzymatic modulation of hyaluronan alters ECS diffusivity and reduces α-synuclein load, suggesting that ECM components actively influence disease progression. Although the reversibility and clinical efficacy of ECM-targeted interventions remain to be fully established, approaches such as enzymatic remodeling of ECM, stabilization of hyaluronan networks, or modulation of astrocytic volume dynamics hold potential to restore healthy ECS properties (17, 22). Understanding ECS remodelling could improve the delivery of therapeutics, including gene therapies and nanocarriers designed to penetrate the brain extracellular milieu more effectively (13). Elucidating ECS dynamics will deepen our understanding of synucleinopathy pathophysiology and guide the development of innovative treatments.

Conclusions

These studies reveal that the ECS undergoes dynamic remodelling in synucleinopathies, characterized by an increase in ECS volume and enhanced molecular diffusion. This expansion results from ECM degradation, particularly of hyaluronan, and intracellular alpha-synuclein aggregates influencing cellular and glial morphology.

Such ECS alterations may both facilitate the clearance of toxic proteins and promote the spread of pathogenic species, while also affecting synaptic signalling and neural network function. These findings challenge the traditional view of ECS constriction in neurodegeneration and highlight the ECS as an active participant in disease progression.

Targeting ECM components or astrocytic dynamics to restore ECS integrity represents a promising therapeutic approach. Future work integrating advanced imaging and molecular techniques is essential to map ECS changes across brain regions and disease stages, ultimately guiding the development of novel treatments.

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The contemporary world of fast-paced (neuro)science

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Born and raised in Portugal, Rui Rodrigues holds a PhD from the University of Lisbon (Portugal) and is currently a postdoctoral fellow at the Marsicano lab, Neurocentre Magendie. His current research is centered on understanding how neural circuits control defensive behaviors and what the mechanisms are underlying susceptibility to stress and psychiatric disorders. He enjoys collaborating in multidisciplinary teams, envisioning new projects and addressing scientific questions, while also making science more accessible to the public.

Science is moving too fast now. As a postdoctoral fellow in neuroscience, I often find myself caught between two main (among many other) competing forces. On one hand, there is the curiosity, fascination, and complexity that drew me in in the first place and that keep me wanting to explore the mysteries of the brain. On the other hand, there is the increasing pressure to publish and build a steady track-record that signals productivity, impact and excellence above all else. And the faster, the better!

The toll of "fast science"

This predicament is not exclusive to me or to my direct peers, or particularly unique to any local academic ecosystem. Recent articles have highlighted a growing concern within the entire scientific community about the culture of speed in academia (1). The world's urgency is overflowing into science, and it hurts researchers and science itself. It leads to an ever-increasing pace of academic activities, a personal toll on the lives of many aspiring scientists and, perhaps more importantly, to the erosion of due diligence, creativity and intellectual risk-taking. This culture of "fast science" is harming science by pushing for perfect curricula (CVs) in short periods, for quantity over quality, and this, in turn, jeopardizes not only the careers of many individuals, as well as their wellbeing, but also the integrity of scientific discovery itself (1,2). The nature of science and research, that inherently requires long, iterative experiments and careful interpretation, is particularly incompatible with this accelerated model. Still, (neuro)scientists keep on adapting to this harsh "publish or perish" system.

The main consequences deriving from such fast-paced culture are anticipation and individualization (3). Researchers, and especially early career scientists, nowadays live in a frenetic anticipatory orientation that suggests that no matter how much they do, it might never be enough. The constant uncertainty allied with the metric-based competition leads to a latent individualization, i.e., a phenomenon whereby researchers' current choices are guided by the anticipated demands of their future selves, that shapes their actions and relationships with colleagues and institutions (3). Accordingly, in this "survival of the fittest" environment, conversations with peers are often punctuated by interrogations

about contracts, paper submission deadlines, evaluation metrics and, more generally, on the fear of falling behind in a system where one's worth is often equated with what one is/was able to achieve during their early career years (4).

The business of academic publishing

This is not just a problem confined to labs and universities. It is tightly bound to the broader structure of academic publishing itself, an industry whose interests do not always align with the nature and core values of science or scientists. Academic publishing has become an extremely profitable industry, with revenues and margins that outperform even tech giants (5). Publishing companies benefit from a system in which researchers not only produce the content with taxpayer (and private) money and peer-review it for free but then must often pay to publish it and buy it back through subscriptions. This circular, insanely-lucrative model, that was firstly designed "for the good of the community", has now turned into a cycle of pro bono work that pushes scientists to do more, to publish more, to review more, in order to boost their curricula (6). Thus, naturally, increasing the volume of publications benefits both parties: researchers academically and publishers financially, even if it comes at the expense of rigor, reproducibility, and genuine scientific progress.

Since the clock is ticking for early career researchers, the incentive to do more has fueled a systemic arms race of productivity. Scientists are publishing far more papers than ever before, and this overproduction is contributing to a proliferation of weak, redundant, and sometimes unreliable studies (7,8). The pressure to constantly generate papers not only leads to fragmented research narratives, but also to a climate where publishing fast is prized over taking the time to build meaningful, coherent contributions to knowledge. This impacts not only the scientific system per se but all its players, especially the careers of thousands of researchers.

The ramifications of "fast science"

Moreover, this culture is not just an internal problem. It has external, more generalized, consequences. From predatory journals and AI-generated papers to citation cartels and paper mills – the threats to genuine scientific discovery are distressing, to say the least (9–11). In particular, the growing issue of paper mills represents an alarming symptom of what happens when academic output is prized over authenticity. Paper mills, i.e., entities that produce fraudulent, manipulated, or poor-quality research articles and then sell authorships, are thriving in this climate (12). Recent investigative reporting revealed how these operations continue to infiltrate reputable journals, sometimes publishing hundreds of papers in fields like neuroscience (11). When we create systems that value metrics and publication number, we inadvertently open the door for unethical practices. This is particularly alluring to early career researchers. The pressure to publish can push some toward questionable shortcuts or temptations. Overall, there is little room in the current system for negative results, for exploratory work that does not immediately yield high-impact papers, or for deep thinking that might lead to conceptual breakthroughs years down the line.

Cultivating slow productivity

Not all hope is lost. An emerging vision on the need for change is boiling (13,14). Rather than accepting the performative pace of academic life as inevitable, we might instead embrace a philosophy of "slow productivity" (15). This does not mean working less or caring less, but rather working better: creating

space for reflection, allowing ideas to mature, and valuing quality over speed. Moving to open-ended and stackable publications or community-based reviewing might be solutions to be considered (16). Science requires time, hard work and patience. Major discoveries are often the product of years of failed experiments, re-working hypotheses and re-thinking old assumptions and dogmas. When we rush, we risk missing what matters most, perhaps important details or new avenues of research, along the way. Therefore, a culture that prizes immediate results over cumulative, well-thought work not only undermines individuals, but it may also stall scientific progress.

I'm not naïve to the realities of academic careers: metrics matter, and jobs remain scarce, as in all other professions. Perhaps we can start to shift what we value within our own academic ecosystems. A shout-out to researchers, universities and funding agencies around the world: advocate for lab cultures where deep thinking and slow, careful science are encouraged; create research programs and funding mechanisms that support early career scientists in taking time to develop skills, to think, to fail; foster critical thinking and rigor over "trendy" and speedy science.

Reaching a balance

Some of the most important papers in neuroscience history would never have made it through today's accelerated production and review cycles. Iconic discoveries like the resting membrane potential or "place" cells emerged not from high-throughput publication pipelines, but from meticulous, slow work by scientists who had the luxury of thinking. Perhaps it is time we made thinking or "failing" as visible and acknowledged a part of our academic output as publishing. Conferences could feature sessions on failed experiments or open questions rather than only polished stories, although this may increase information overload. Journals could dedicate space for thoughtful essays and theoretical perspectives without immediate data. Evaluation committees could (which I think they are starting to) weigh intellectual contributions, ancillary activities, advocacy/outreach, and collaborative mentorship alongside publication and citation counts.

Over the last years, several key initiatives have emerged to counterbalance this "fast science" phenomenon and promote open science, rigor and transparency. For example, the open-access journal eLife has pioneered new peer review models, such as consultative peer review and transparent decision letters, to improve the quality and openness of scientific evaluation (17); this model, although far from perfect, fostered discussion around peer review practices. Similarly, the Declaration on Research Assessment (DORA, https://sfdora.org/read/), that advocates for responsible research assessment practices and encourages researchers to move beyond journal-based metrics (like journal's impact factors), has been instigating a more equitable and fairer academic ecosystem. Additionally, Plan S, spearheaded by cOAlition S (https://www.coalition-s.org/about/), a consortium of national research funders and charitable foundations, requires that publicly funded research is published in compliant open-access journals or platforms, fostering immediacy and transparency in academic publishing. We cannot solve the structural problems of academia overnight, but we can start by identifying them, and nurturing practices that support early career researchers and allow slower, more meaningful neuroscience. In the end, the questions we are asking about the brain deserve nothing less.

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Rethinking autism and intelligence: is the brilliant antisocial mind an actual thing?

Juan García-Ruiz[1]
[1] Magendie, University of Bordeaux

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.

The film industry, TV shows, and social media have long popularized the old stereotype of the highly intelligent but socially impaired individual. You probably have examples in mind, like Sheldon Cooper from *The Big Bang Theory* or Dr. Shaun Murphy from *The Good Doctor*. Even historical figures like Charles Darwin and Albert Einstein are often retrospectively associated with autism, even though they were never diagnosed during their lifetimes. The idea of the *autistic savant*, also known as *savant syndrome*, is not new. It's a condition where a person with disabilities shows exceptional skills in specific areas. But does autism really come with higher intelligence, or is this just a persistent myth?

To make sure we are on the same page, let's go back to the definition of Autism Spectrum Disorder (ASD) actually is. The diagnosis of autism requires the presence of **difficulties in social interaction and communication**, and **restricted or repetitive behaviors and interests**.

Specifically, individuals with autism may struggle to understand typical social cues, maintain eye contact, or form and maintain relationships. For example, an autistic child might show an impaired theory of mind (the cognitive ability that allows us to understand other people's desires, intentions, or emotional states). This could make it difficult for them to guess whether another child would prefer one scoop of ice cream or two. After all, it's not their preference, *so how could they know*?

When it comes to repetitive behaviors or focused interests, these can be very varied. Taking the earlier example of Sheldon Cooper, his fascination with trains and his strict habit of knocking exactly three times on a door illustrate these patterns pretty well.

Autism is diagnosed more frequently in boys and men than in girls and women. That opens up a whole separate discussion that may be discussed in a future article. But in short, gendered expectations around behavior, as well as different ways of coping with symptoms, often lead girls and women to hide their difficulties. As a result, they're more likely to be overlooked and underdiagnosed. Autism is

typically identified in childhood, which is why it's classified as a neurodevelopmental disorder. However, adults can also be autistic, even if public perception still tends to focus on young boys and girls.

According to the World Health Organization, about 1 in 100 people are autistic, though this is likely a conservative global estimate. When we look at individual countries, the numbers vary widely. This variation can be explained by factors such as the diagnostic manual used (for example, the ICD in Europe versus the DSM in the States), levels of stigma and awareness (with lower reported diagnoses in Eastern and Southern Europe), differences in healthcare access, as well as socioeconomic conditions.

Do autistic children really have higher intellectual abilities?

The short answer: not really. Intellectual abilities among autistic individuals are highly variable. Just like in non-autistic populations, there's no single pattern. Intelligence in autism spans the full range, from intellectual disability to giftedness. Although exact numbers vary across studies, current research indicates that there is a bimodal IQ distribution in ASD, which means there is a clustering of individuals with below-average IQ, and another clustering with above-average IQ. Importantly, intellectual disability co-occurs with autism in more than one-third of cases, which highlights the need to move beyond stereotypes and adopt a more nuanced understanding of the condition.

It's also worth clarifying that savant syndrome is not the same as having above-average intelligence. Savant syndrome is an extremely rare phenomenon in which an individual, sometimes even with cognitive impairments, displays extraordinary abilities in very specific areas, often referred to as *islands of genius* (like exceptional musical or mathematical skills). These abilities are usually isolated and don't reflect overall intellectual functioning.

The key takeaway is that while some autistic individuals may have above-average intelligence or even savant syndrome, these cases are definitely not the rule.

Where do these misconceptions come from?

It's true that some autistic individuals are considered savants (up to 10%, as mentioned earlier), showing extraordinary abilities in areas like mathematics, art, or music. But non-autistic people can also have these rare abilities, and they are just as uncommon. These exceptional skills are not a defining feature of ASD, but when they do happen to co-occur with autism, they tend to draw disproportionate attention and media coverage, which can distort public perception and make these cases seem more common than they are. There's a clear bias towards success stories that are showcased in the media because they are more appealing and easier to sell than everyday realities involving low or average cognitive performance. One well-known example is Temple Grandin, an American academic who made *Time* magazine's list of the 100 most influential people in 2010 and has written extensively about her experience living with autism.

However, the root of this misconception might come from the very origin of the conceptualization of autism. In 1940s, physicians Leo Kanner and Hans Asperger, independently described what we now recognize as autism. An important difference between Kanner's description of autism and Asperger's one was the cognitive and linguistic skills. Indeed, Asperger highlighted the great grammatical abilities and early language acquisition among his patients, contrasting with the observations of Kanner that often included language impairments. This led to the inclusion of Asperger Syndrome in the diagnostic nomenclature in both the ICD-10 (1992) and the DSM-IV (1994). However, this distinction is no longer used, as ICD and DSM removed Asperger Syndrome as a separate diagnosis.

In short, our misconceptions about autism and high intelligence likely stem from a combination of media narratives, the historical influence of Asperger in the conceptualization of autism, and our own cognitive biases. As these misconceptions persist, we need to challenge and rethink them.

Why is it important to debunk the autistic genius cliché?

Highlighting the reality behind the autistic genius stereotype is crucial. Not just because it distorts the reality of autism, but because it can cause real harm to those it claims to represent. This myth misrepresents the true diversity of autistic experiences and creates unrealistic expectations. And promoting this cliché can have actual consequences on people lives, as it fuels discrimination, bullying and social exclusion. By focusing on rare stories of genius, we risk overlooking the everyday challenges many autistic people face, and with that, we risk failing to provide the support they need.

If you're looking for another reason to move beyond the autistic genius cliché, an idea partly rooted in Hans Asperger's original descriptions, it's important to acknowledge the ethical controversy surrounding his legacy. Historical research has shown that during the Nazi era, Asperger participated in programs that classified some children as "uneducable" or "lives unworthy of life," resulting in their transfer to killing centers. This does not erase his scientific work, but it has led to serious re-evaluation of the term "Asperger syndrome" and its appropriateness (both ethically and scientifically).

From the academic and the clinical side, efforts have been done to abandon simplistic labels like low- and high-functioning autism, which fail to capture the complexity of the condition. Today, the DSM-5 defines three levels of autism severity based on the amount of support required (from level 1 requiring some support to 3 requiring a very substantial support for most severe forms). But real change doesn't stop at diagnosis. To cultivate an accepting society, common efforts are required, and this includes continued public education to dispel myths (you can for instance share this great article you are reading right now), the promotion of diverse representation in media, and the consistent advocacy for individualized support considering the needs and strengths of each person with ASD.

Only when individuals are truly understood, included, and empowered can society benefit from their unique perspectives and talents.

Women's Voices: inspiring the neuroscientist community

Olga Barba Vila

Sara Carracedo[1]
[1]Institute of neurodegenerative diseases (IMN), University of Bordeaux

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 feature **Olga Barba Vila**, a PhD student at the IINS and an active member of the NeuroPIC. Originally from a small village in Catalonia, Olga studied Biomedical Sciences in Barcelona. Her academic journey brought her to France, where she joined the NeuroBIM Neurosciences Master's program and later began her PhD at the IINS working on sensory processing in the gustatory cortex. In this interview, she reflects on her academic path and discusses the challenges and hopes for achieving gender equity in science across Europe.

Sara Carracedo: Could you please introduce yourself and provide a brief background about your academic journey?

Olga Barba Vila: My name is Olga, and I am from a small village in the heart of Catalonia, Spain. From a young age, I have been passionate about the human sciences, which led me to pursue a degree in Biomedical Sciences at the Autonomous University of Barcelona (UAB). During this time, I discovered my true calling in neuroscience research, a realization that was confirmed during an internship with the Neuroplasticity and Regeneration Group at UAB's Neuroscience Institute.

To further specialize, I moved to France to pursue the Bordeaux International Master of Neuroscience (NeuroBIM). There, I developed a growing interest in circuit neuroscience and had the opportunity to complete two internships in laboratories in France and Sweden. These experiences solidified my interest in systems neuroscience, particularly in understanding how neuronal circuits process complex information. This led me to begin my PhD in 2022 under the supervision of Mario Carta in the team

“Synapses and Neural Circuits in Behaviour” at the Interdisciplinary Institute for Neuroscience (IINS), University of Bordeaux, France.

Sara Carracedo: Could you tell us more about your current research focus?

Olga Barba Vila: I am currently in the fourth year of my PhD, focusing on how the cortex encodes gustatory information. The gustatory cortex (GC) enables animals to identify the identity of food and its hedonic value, for example, palatable (e.g., sucrose) versus aversive (e.g., citric acid), which is crucial for avoiding poisons and regulating feeding behaviors. Despite its importance, the neuronal circuits within the gustatory cortex are not as well understood as those in other sensory systems, such as touch or vision.

In my PhD project, I use a combination of ex vivo slice electrophysiology, optogenetics, and activity reporters in mice to explore how the GC receives and integrates information. Specifically, I am investigating the synaptic inputs that the GC receives from the gustatory thalamus (VPMpc), which provides information on tastant identity, and from the amygdala (BLA), which conveys the hedonic value of these tastants. My goal is to uncover how these inputs are processed at the synaptic and circuit levels within layer 5 pyramidal neurons, which are the primary output neurons of the cortex and are optimally positioned to integrate gustatory information.

Sara Carracedo: What accomplishments have you achieved during your PhD so far?

Olga Barba Vila: During my PhD, I have reached several key milestones. Early on, I was awarded a PhD fellowship from the Bordeaux Neurocampus Graduate Program, which allowed me to pursue my PhD with the team I had aimed to join.

I co-authored a Journal Club publication in the Journal of Neuroscience, where we discussed the research of a leading group in the gustatory cortex field. Over the course of my PhD, I have had the chance to present my work at several national and international major conferences, including NeuroFrance in Lyon (2023) and the FENS Forum in Vienna (2024).

Throughout my PhD, I’ve also learned several challenging techniques, such as patch clamp electrophysiology, which has been critical to my research. Additionally, I have had the rewarding experience of supervising several students, and guiding them has been one of the highlights of my PhD journey so far.

Sara Carracedo: You are part of the Neurocampus Parity Committee, what motivated you to join this group? Which initiatives from this committee do you think are particularly important?

Olga Barba Vila: Witnessing the alarming statistics that highlight the unacceptable gender inequality in science, particularly at the Bordeaux Neurocampus, left me deeply concerned and feeling helpless. For instance, the 2022 gender equality survey conducted in the Bordeaux Neurocampus by the Neurocampus Parity Committee revealed that women represent only 38% of young tenured researchers and a mere 25% of senior researchers. Additionally, 79% of the 72 leaders heading 54 research teams are men . This concern drove me to join the NeuroPIC, as it offered an opportunity to contribute to change, even if only on a small and local scale.

I find all the initiatives and goals of the NeuroPIC highly relevant, as they tackle gender inequality at multiple levels. Among many others, these actions include monitoring the current state of inequality

and its evolution over time, organizing events, and providing training and mentoring to empower female researchers and raise awareness within the scientific community.

[1] NPC 2022 Gender Equality Survey

(https://www.bordeaux-neurocampus.fr/wp content/uploads/2023/06/CPN_2023_report_en_final.pdf)

Sara Carracedo: As an early career researcher who has worked in laboratories from different countries in Europe, how do you see the international picture of women in science?

Olga Barba Vila: Like many other sociological aspects of life, there are noticeable differences in the role of women in science depending on the country. One of the aspects I appreciated the most about working in Northern European countries was the comparatively smaller, though still present, gender inequalities faced by women in the Swedish research environment, as opposed to those encountered by women working in Spain, for example. Unfortunately, although I have not experienced this myself, the gender gap is even more pronounced in less developed countries, where women's opportunities are often limited at even earlier stages of their careers.

Sara Carracedo: What advice would you give to young women aspiring to enter into a PhD program?

Olga Barba Vila: My advice to young women aspiring to enter a PhD program is to remain hopeful that the deeply rooted system that permits gender inequality will eventually fade. I encourage them to stand up for their rights and what they deserve, and if they find it difficult, to seek help in doing so.

I want them to remember that any feelings of inadequacy or self-doubt they may encounter during their academic journey rarely reflect their true capabilities. Instead, these feelings are usually the result of a biased system, both socially and institutionally. Rather than questioning their worth, they should focus on their strengths and seek out supportive mentors and networks. And if they have the strength, I encourage them to join us in working toward an academic environment free of gender bias! 😊

NeuroPath: exploring careers beyond academia

Florian Hontarrede, clinical research associate

Aude Verboven [1]
[1]IMN, University of Bordeaux

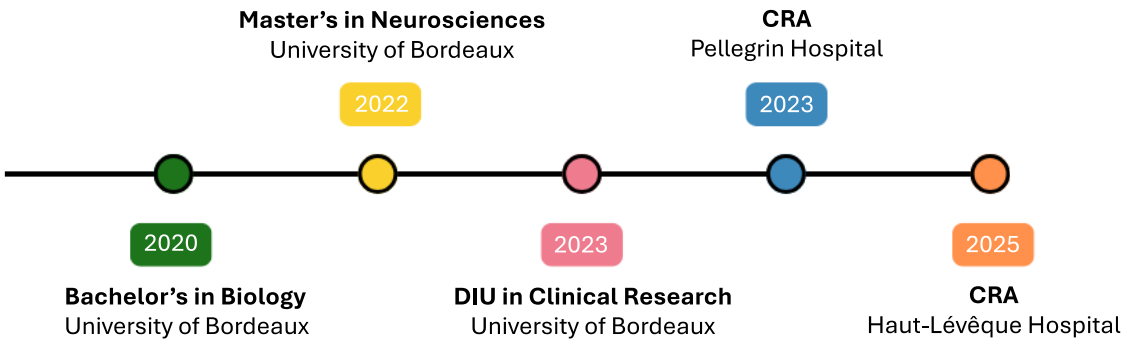
The world of science offers many exciting paths, and academia is just one of them. Each year, both the public and private sectors actively seek PhD graduates to fill diverse roles. However, many of them may seem unfamiliar to most of us. At Brainstorm, we want to help you explore career options that 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 interview Florian Hontarrede, who previously did an internship at the NutriNeuro lab, before heading toward clinical research. Florian is now a clinical research associate at Haut-Lévèque hospital, working in the reference center for rare diseases. Carrying out various clinical study projects, he acts as a link between patients, healthcare team and institutions, ensuring constant compliance with the regulations governing this field.

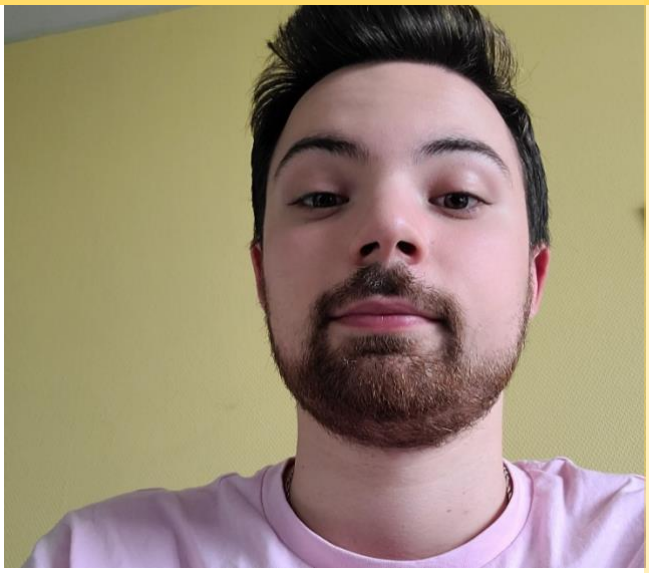


Are you interested in knowing more about the clinical research associate job as a career path? Then this section is for you!

Clinical research associate (CRA)

Florian Hontarrede

"We are the pillars of clinical research within healthcare team. "



Why you decided to choose this professional path?

I did not want to engage in a PhD but wanted to stay in research. This job allows me to stay in research but with less pressure than academia and without working on animals. I find the research on humans really enriching.

Match interests and soft skills

You need to be rigorous and organized. Also to like the contact with people and not be scared of seeing difficult things.

Advice for PhDs interested to apply to this type of job?

Keep your curiosity, it makes the experience more interesting!

Main tasks

- Ensuring compliance with clinical trial regulations
- Communicate with patients
- Administrative and a few financial tasks
- Database management
- Link between patients and the healthcare team in clinical trials

Pre-Requirements

Minimum of a Bachelor's degree in a scientific field.

Basic knowledge in biology.

Good interpersonal skills. Autonomous and rigorous.

Professional development

Possibility to change working environments: CRA roles can vary significantly between teams. Opportunities to grow into roles such as Clinical Trial Manager, Research Engineer, or Clinical Trial Project Manager.

Working conditions

Work environment: mainly office job inside hospitals, possible to work from home.

Pressure level: Moderate to low

Work-life balance: Very good.

Salary: Suitable for early career but slow to develop

Do you have further questions?

Contact Florian at florian.hontarrede@chu-bordeaux.fr

From neural wiring to behavior

Interview with Brian Chen

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'm going to remind you of something you already knew: nature is fascinating. Who hasn't been amazed by the synchronized flight of starlings? Or by the skilled spiders when they spin their webs? No less impressive are the dances of bees to communicate with each other when they find a source of food. But what is really fascinating is not the ability of these animals to perform these behaviors. Starlings don't need to spend hours in the library to learn to coordinate with their own kind, nor do spiders need to watch sewing tutorials, nor do bees need dance lessons. What's really fascinating is our ineptitude! But are we really inept? No! That's what I try to tell myself when for the fourth year in a row I play the same Chopin waltz on the piano, each time achieving an improvement imperceptible to the human ear. Both spider web weaving and virtuoso piano playing are behaviors bordering on divinity. However, the former is an innate behavior and therefore needs no conscious learning and the latter —unfortunately— is an acquired behavior that needs years and years of practice. For an innate behavior to occur and be repeated generation after generation, the brain of each individual must follow the same set of recipes. So, although each brain is a world and the connections between neurons vary between individuals, there is also a basic wiring that reminds us that we are also the same. I could go on writing about how amazing the piano is, but you've come this far to learn something about brain wiring and about science. So let's talk a bit with Brian.

Brian Chen is an Associate Professor in Neuroscience at McGill University. He started his lab at McGill University in 2009. Chen performed his graduate work with Dr. Karel Svoboda at Cold Spring Harbor Laboratory and then worked with Dr. Dietmar Schmucker at the Dana-Farber Cancer Institute and then Dr. Josh Sanes at Harvard University for his postdoctoral research.

Juan García Ruiz: What brought you to do research?

Brian Chen: As a child, I admired how ancient philosophers spent much of their time thinking and trying to answer deep questions about how the world works. Eventually I learned that modern science was the same pursuit, where I could spend much of my time thinking and trying to answer deep questions. I had a love of nature and the outdoors growing up, and was fascinated by the natural world, in particular animal behavior. As an undergraduate student, I sought to study animal behavior and this led me to neurobiology. There, I did research on the auditory system of bats. As a graduate student, I studied experience-dependent plasticity in rodents, specifically, how anatomical changes in neurons accompany electrical changes in their receptive fields. I had so much fun doing research as a student that I decided to pursue it as a career path.

JGR: What is your research about?

BC: The question that drives me the most is how an animal can perform complex behaviors without any learning or prior experience. There are so many amazing and beautiful things that the animal kingdom can do without learning, from our own simple pain reflexes to very complex insect behaviors that are performed as soon as the animal is born. In other words, how are the hard-wired neural circuits that underlie these innate behaviours wired up?

Obviously, all of the instructions required to wire up these neural circuits have to be embedded somehow in the animal's genome. My goal is to decipher these molecular instructions to understand how to go from molecules to fully connected and functioning neural circuit. Right now, I am trying to identify a list of molecules that are necessary and sufficient to wire up a neural circuit in the fruit fly *Drosophila melanogaster*. If I can identify a list of molecules that I can take and put into another neuron and re-wire it to change an animal's perception and behavior, then I feel I would be on the first step to understanding how to wire up a neural circuit. Yes, I am starting with a single neuron, before moving to a full neural circuit, which is far from an entire brain, but it is a difficult problem. As I said, I like answering deep questions.

JGR: How do you study neural circuits, in a nutshell?

BC: We mostly use the fruit fly *Drosophila melanogaster* as an animal model to study neural circuits. We use the fly because of its advantages in genetics from the past 100 years as a genetic model organism, and its track record as an exceptional model system for studying neural circuits. The main techniques we use are high-resolution imaging of single neurons, single cell RNA sequencing (so we can identify molecules used for wiring inside a single neuron), and then lots of other clever molecular biology and molecular genetics tricks that *Drosophila* allows for, or makes easier, like CRISPR-Cas9 genome editing or single neuron genetic knockouts. We occasionally investigate how these molecules function in the context of the mammalian brain using mice and also human neurons from stem cells in cell culture.

JGR: To which extent we can learn about our wiring from animal models?

BC: Over 60% of the Drosophila genome is homologous to the human genome, and much of the pioneering work on identifying and characterizing brain wiring molecules was performed using Drosophila melanogaster as an animal model. We would understand very little about our own brain wiring without the use of animal models throughout the long history of neurobiology. Classic experiments using models as Drosophila melanogaster, grasshoppers, chicken embryos, zebrafish, frog tadpoles, rats, and mice, produced ground-breaking science that revealed fundamental principles underlying how brains wire up that would not have been possible without animal models.

And that would be my simplistic answer to your question, but I appreciate that this is a particularly insightful question, because it is specifically about brain wiring and not just brain function. Figuring out how the human brain works, the most complicated machine in the known universe, is already hard enough without animal models. Right? Because human brains are all but off limits to invasive research—you don't have easy access to a human brain, and I'm not just talking about the skull, you can't take samples of living brain tissue either, you can't perform whole cell patch-clamp recordings in a human brain, you can't delete one area and over-excite another and see what happens, you can't just root around inside someone's brain, because all of those things are unethical because our brains are who we are. So it's hard enough studying how the human brain functions without the use of animal models.

But, you asked about our brain wiring. A complete contrarian could say that all knowledge about how the human brain is wired that comes from animal models are completely irrelevant and useless, because they come from animals that are not *Homo sapiens*. Thus, we can only use human brains to study human brains. Or you can say, well, regardless of whether animal models are relevant to human brain wiring or not, I will only use human brains. From there you can

basically only use human genetic association studies, where variations or mutations in genes cause wiring phenotypes in humans with diseases, disorders, or differences that manifest visibly, in other words, very obvious clinical signs. Beyond that, again since we are talking about how brains are wired, and this means molecules, you can only manipulate these molecules in human neurons from stem cells in a dish and then see what happens. At best you could manipulate human neurons in a tissue organoid in a dish, and that's pretty much it. And that's it, there's nothing beyond that. No behavior, no natural or complex circuitry, no functional output from a brain. So essentially, what I'm saying is that there is no other way!

I really liked the question because it made me think about the unique problems associated not just with doing neurobiology, but in particular with molecular neurobiology.

JGR: Why is it relevant to understand nervous system wiring?

BC: Understanding how nervous systems in general are wired is important and relevant because it deepens our understanding of the animal kingdom, and the how and the why of animal behavior, including for humans. For example, understanding how genes control wiring is relevant to human disabilities associated with brain wiring such as autism or schizophrenia, and for re-wiring of damaged nervous tissues. Thus, future applications could include enhancing the neural capabilities of those with mental disabilities, or recovering from damage to the nervous system.

JGR: Understanding of the instructions of nervous system wiring is a tricky task, but do we have the knowledge and means to go from understanding to build a brain or for the moment it's still an ambitious aim?

BC: It is definitely an ambitious aim at the moment! The main obstacles are the vast complexity of genomes, whether it is *Drosophila melanogaster* or human, and the vast complexity of neural circuits. So for example, in a single neuron you could have thousands of different molecules working to allow the neuron to function properly and that comes from the complexity of the genome, with thousands of genes being active at any given moment in time, and then even in a simple neural circuit in an animal you can have fifty neurons and thousands of connections amongst them.

JGR: You have created a bioinformatics database. What is GeneDig?

BC: GeneDig is a web application that I developed for easy and efficient access to genomics data and analysis. As I mentioned, genomes are very complex because they are large (at billions of letter codes), they contain DNA and RNA and protein information, and there are lots of genomes that are sequenced, from coronaviruses, to bacteria, fungi, plants, animals, humans, and individual humans as well. This makes it very complicated to understand or even access the most basic genomic information, like what genes are involved in a certain disease and what are the DNA, RNA, and protein sequences for that gene?

As a postdoc, I found it frustrating to use the publicly available, ridiculously complex databases just to get the RNA sequences for a gene to do some basic experiments. Once I figured out how to do it, once I started my own lab, I still had to train people each time on how to do what should be easy, basic, bioinformatics tasks. Let's say I have a patient mutation in a disease gene that I would like to recreate in the lab to investigate. Finding the sequence of a gene using the public databases is very hard for a high-school or undergraduate. Then, you have to locate the site of the mutation, then find the RNA sequence, and then how the DNA and the RNA and the protein all line up together to design your experiments to recreate the mutation. Trying to convert this into the mouse or fly homolog is even harder! Similarly, doing any protein structure-function work is equally painful, going from amino acid to RNA, let alone how that relates to the genomic DNA. Those examples are each about 20 bioinformatics steps that use about 20 different databases and websites, that each take half an hour to an hour to resolve, but takes GeneDig a few seconds.

I created GeneDig to solve all of these problems. Back then I realized that meaningful access to genomic and bioinformatics information was super important and only going to get more important in the future. So, my goal with GeneDig is to make all genomic information easily accessible and useful. I downloaded all of the publicly available sequences onto my servers, all of the disease information, all of the chromosome information, everything I could find. Then from GeneDig, you can simply type in any gene or disease into the search box, or change the organism to any sequenced organism to search their genome. Or you can start browsing the chromosomes instantly by just clicking on the name of the organism. Once you start browsing the genome you can see the relationship between disease mutations, DNA sequence, RNA sequence, protein amino acid sequence, and protein domain altogether.

GeneDig isn't really meant for the general public even though I built it with that in mind as a guiding principle. Fortunately, it is often used across the world for biology education, like in Brazil, Indonesia, and India, so I must be doing something right. Unfortunately, I don't have a team working on it, so it's super hard to fix things and roll out new features that I've had in mind.

JGR: What do you like the most about research?

BC: I definitely have the best job in the world! I get to investigate the most complex machine in the known universe and unravel the deepest mysteries of biology. I am definitely very lucky to get to do what I do. I have no boss, I have complete job security, and complete academic freedom, so I can pursue fun things like GeneDig and other exciting projects. I get to lead and interact with a phenomenal team of really smart undergraduate students, graduate students, medical students, postdoctoral fellows, engineers, computer programmers, and technicians. Every day there is something new for me to do and learn about and I am constantly being challenged intellectually and creatively, so what's not to like? On top of that, my colleagues here at McGill are very smart, nice, a lot of fun, and down to earth, very Canadian.

I like to be in lab doing things, so I prioritize time for that. I enjoy meeting with my lab discussing their latest progress and results, doing experiments, performing surgeries and dissections, doing molecular biology, imaging, building new equipment and machines, building new software, and just playing around in general. I balance the projects in the lab in the following order of priority: curiosity-driven and interesting to me (e.g., how hard-wired circuits are wired up), interesting or meaningful to society (e.g., how a disease gene alters a neuron's function), societal utility (e.g., our high-throughput drug screens to identify drugs that alleviate a disease), and inherent beauty (e.g., making an auto-luminescent fruit fly). Thus, the majority of the projects in my lab are driven by curiosity and having fun.

One of my most favorite things about research is the exciting moment when you realize you are the first person to observe your discovery. I felt like that many times in my career and I enjoyed and cherished each time the exciting combination of wonderment and pioneering spirit.

JGR: What would you tell future researchers to improve research quality?

BC: Learn from good scientists, ask a lot of questions, and listen a lot. Always assume you don't know much, and always be willing to learn. Arrogance is the antithesis of science, and once you become arrogant you stop learning. Read lots of different articles on lots of different subjects. Attend lots of seminars on various subjects.

One helpful way to grow is when you are attending seminars in your field. Write down lots of questions you would ask during the seminar, and see if they line up with what others ask during and after the seminar. Discuss the seminar with others. Then see if your questions at other future seminars begin to evolve, from not understanding the material, to curious tangents, to nit-picky details (which are still important), to critical details, to critical experiments with the bigger picture in mind. Look to see whether you can differentiate for yourself whether the questions that you are asking require either a different interpretation of the data, or a different data analysis, or a different experiment entirely. Why is this helpful? In your own science you will then begin to see what the payoff is for your different experiments, and how they affect the big picture outcome. This will help you prioritize your time, energy, and money and allow you to deliver on the more important experiments. In the theoretical world, all experiments are important and every control is important, but in the real world not all experiments are equal, and some are more important than others. Find out which ones will tell you which things about your hypothesis. Find out during seminars which controls and experiments tell which things, and you will be on your way to improving your research quality because you will be thinking deeply about your science.

It is definitely important to be very critical, and to learn a lot about mistakes, fallacies, and sloppiness in science. But I feel that there is no need to emphasize that, because most scientists are already nit-picky and hyper-critical, and some tend to take pride in being negative and destructive. It is very instructive to learn from the hyper-critical though, it is still tremendously helpful.

Here are some more practical tips: This is hard to do, but make sure to continually iterate from experiment to analysis, back to experiment, and let your analysis inform the next round of experiments. Don't wait to pile up a bunch of experimental data before you go over it. I know that lots of scientists love the experimental side of things, and find comfort in the process of doing things with your hands, I certainly do, too. But don't use that as a procrastination method to data analysis. I love this part as well and that's often where the real moment of discovery occurs and it is exciting. You should be putting in at least as many hours in data analysis for every hour of experiment. Stare at primary

data a lot. And I mean a lot. Obsess over it. I still do, and I no longer generate much of the primary data in my lab. Let the data and the science tell you what the biology is.

Here are different exercises we do in my lab a lot. Always know what the purpose of each experiment and control is for, and specifically, what the best case outcome you expect is, the worst case outcome, and the most likely outcome. Plan ahead what you will do in each of these scenarios. Keep in mind that the worst case outcome of an experiments is often not a negative result but a uninterpretable or middling result. Those are the worst. But, if you know ahead of time what each outcome is supposed to tell you about your hypothesis, then you will much more deeply understand your projects. The great thing about this exercise is that it is all just thought experiments that get you better at your science, and they allow you to think multiple steps ahead for your projects. I also have my lab do this for planning everything in life, and thinking about outcomes and what your reaction and next steps will be given different outcomes. It is a very useful and easy habit to pick up.

Another exercise that I do is in lab or in our journal clubs, we examine a project or experiment and start with infinite time, money, and personnel. Then think about all of the possible ideal experiments and controls that you would do if you had infinite time, money, and personnel. The most important thing, again, is to list what each experiment or control will tell you about your hypothesis. This is fun because you can also start to go crazy dreaming about what you would do with lots of money. Still, you also begin to see that there are some points of diminishing returns and that, again, some experiments are more important than others. You will really begin to see what the rationale is for different experiments are, what your holes are in your experiments and how big of a hole it is, or in a journal club paper, and how it ultimately affects the main hypothesis. You can also see more clearly why you may not need a multi-million dollar clinical trial to prove something reasonably.

You will also more easily see how projects can branch off too much and not answer a central question, even with infinite resources. The end of the exercise comes with picking which experiments to do in the lab with the real world constraints of limited time, money, and personnel. Finally, the most painful part of the exercise is estimating realistically how long each experiment will take, and the multiple resources and steps and sub-steps it will take to get it done, and the reality sets in that science takes a lot of time. Nevertheless, this is a fun exercise because it allows you to be very creative and they are just thought experiments. Who doesn't like dreaming of infinite funds?

JGR: Would you like to share a general message to the readers?

BC: Most importantly, thank you for having any interest in my science. If I have helped just one person with my long answers, even subconsciously, then this is more than worth it.

My general message to any readers is to not try and be a good scientist, but a good person. I'm not trying to be generic, so what I mean is, learn as much as you can and as many skills as you can that can be useful to society or somebody. It doesn't matter what the skills and knowledge are to start with. Get extremely good at a few things, and pretty good in lots and lots of other things. Then, go use these skills or knowledge to help someone. You will be pleased with the results.

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