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REVIEW

Functional implications of single-cell identity in the nervous system

Elena Baz Badillo[1]

[1]Interdisciplinary Institute for Neuroscience (IINS), University of Bordeaux

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Elena Baz Badillo

Born in Salamanca (Spain), Elena has a Bachelor's Degree in Biology from the University of Salamanca and she has done the NeuroBIM Msc at the University of Bordeaux. She is currently a second year PhD student at the IINS where she is focused on neurodevelopment, transcriptomics, and synaptic plasticity.

Abstract

Next generation high throughput sequencing technology allows a deep analysis and discovery of subtle yet significant differences across neurons. For most species, neuronal types and subpopulations, characterized morphologically and electrophysiologically, match a cluster defined by a specific gene expression signature. Furthermore, because these techniques allow the simultaneous analysis of thousands of genes and cells, fine differences can be found within the same cell subtype. This raises a growing interest on the understanding of how cells in the nervous system express specific combinations of proteins used as a "molecular ID" to recognize each other and establish functional circuits. In this review, I will discuss how different layers of cell identity are involved in the correct functioning of the nervous system and how this diversity is favored both during evolution and development.

Keywords

Single cell RNA sequencing, cell identity, neuronal subpopulation, circuit development, cell-cell interaction.

Introduction

The effect of natural selection over millions of years has driven unicellular organisms towards multicellularity with highly specialized cell types which cooperate to achieve an excellent adaptation to their unique environments. In mammals, the degree of specialization is astonishing and several layers of cell identity can be distinguished. During perinatal development, stem cells regulate their gene expression to achieve a specific cell type identity. In highly complex and heterogeneous systems, such as the nervous system or the immune system, cells can also be part of specific subpopulations. These subpopulations are defined not only phenotypically, but also by the expression of discrete gene signatures.

In the nervous system, neurons and glial cells are embedded in highly specific circuits. Information in the shape of electrochemical signals travels across various neurons, giving rise to the wide range of cognitive functions and behavior observed in mammals. The final objective is for the organism to be better adapted to its environment; hence, circuits responsible for producing an adapted response need to be as precise as their outcome itself. An example of these stable, conserved, and precise neuronal circuits are memory engrams: structured groups of interconnected neurons that give rise to specific cognitive outcomes (1). Thus, it cannot be said that neurons assemble into these circuits randomly, or as proposed by Peter's rule (2), by simple pre- and postsynaptic partner apposition. In fact, the assembly of neuronal circuits during development seems to respond to a precise, coordinated, and multifactorial regulation. First, neurons must be able to recognize each other within the complexity of the nervous tissue. Therefore, cell-cell recognition is essential, since it allows neurons to establish connections with the most appropriate partners and, at the same time, reject the suboptimal ones. This phenomenon is known as "synaptic specificity" (3). The two main mechanisms that have been proposed to regulate synaptic specificity are, on the one hand, an activity-dependent selection, such as Hebbian plasticity, but also predefined, genetically encoded clues, in the line of Sperry's chemoaffinity hypothesis. Both hypotheses are supported by experimental evidence (4–6), which suggests an interplay between both mechanisms.

However, the identification of differences in gene expression between individual cells has remained elusive for years. Recent technical advances in transcriptomics, such as single-cell RNA sequencing, has allowed researchers to not only confirm the identity of neuronal subpopulations that had been previously described according to their phenotype, but also to reveal more subtle differences among them and, therefore, define new cellular subtypes (7). Moreover, because thousands of cells and their transcriptomes can be accessed simultaneously, it is now possible to analyze individual differences within a single cell subtype and therefore point at possible candidates encoding single-cell identity and, in turn, its connectivity

This review aims to discuss different layers of cell identity in the nervous system – from cell type to subpopulation to single-cell –, and the possible functional implications of each during development and wiring of neuronal circuits. Additionally, I will briefly describe which are the features should a protein family have to be considered as a candidate for connectivity encoder. Finally, these attributes will be illustrated discussing the possible function of clustered protocadherins (cPCDH) in the developing cerebellum.

Methods

For this review, original and review articles were accessed through PubMed (https://pubmed.ncbi.nlm.nih.gov/). The original searches performed, in the nomenclature used in this database, were:

"((neuron) AND (cell identity)) AND (review[Publication Type])", "((synaptic specificity)) AND (review[Publication Type])", "((neuron) AND (subpopulation)) AND (review[Publication Type])". Reviews from 2015 and onwards were selected. From this first bibliographic approach, original research articles were found through the references of these reviews.

Results

CELL TYPE DEFINITION

According to the classical textbook definition, cells are the basic, independent unit of life. In the case of multicellular organisms, the appearance of groups of similar cells working cooperatively towards one specific function had been critical for their evolution. It allowed them to adapt to their environments extremely efficiently in comparison to unicellular beings. The diversity of cell types has changed over evolution, and it is possible to trace an evolutionary relationship between different cell types: both intra- and interspecies (8). Importantly, evolutionary connections of different cell types must be accounted for since their characteristics are heritable, and thus the subject of natural selection. Nevertheless, in a majority of cases, a simple phenotypical classification is done following the original description of each cell type (based on morphology and function). Regarding this matter, in 2016, Arendt et al. proposed the following evolutionary definition of cell type: "a set of cells in an organism that change in evolution together, partially independent of other cells, and are evolutionarily more closely related to each other than to other cells. […] Cell types are evolutionary units with the potential for independent evolutionary change". As the authors explain, this definition implies the existence of genetic information used by a given cell type and not necessarily by others. In this sense, it is important to explore the molecular identity shared by the cells belonging to a certain cell type, which is currently a growing research topic (19931 articles and review articles containing single-cell RNA sequencing approaches have been published in the last 10 years according to PubMed); in part, due to the relative accessibility and development of single-cell RNA sequencing-based technology. Conclusively, cell types ought to be considered as evolutionary units in a global context and, as such, genetic variability among cell types can be the subject of natural selection. Furthermore, these genetic specificities might be described using high-throughput transcriptomics methods

Cell type engagement during development

After discussing the importance of cell types diversity in the geological timescale, a fundamental question still remains at the level of single organisms: how do stem cells, with their capacity to differentiate into a broad variety of cell types, choose their fate? While they are able to access virtually the same genetic material, stem cells are exposed to various differentiation-inducing signals during development. These signals activate a heterogeneous range of developmental signaling cascades; i.e., different cells respond diversely to these signals, which leads to engagement in a specific differentiation program. It has been proposed that this phenomenon is highly dependent on the so-called "terminal selectors". These are a reduced series of transcription factors able to regulate the co-expression of a great percentage of cell type specific genes. This is not only true for the differentiation process of neurons, but also for the maintenance of cell type identity in postmitotic neurons (including expression of neurotransmitter synthesis enzymes and receptors, ion channels and other key molecules for neuronal function) (8–10). Drosophila optic lobes are an especially convenient model for the study of cell type specific differences. They contain around 60000 neurons per lobe distributed in 200 morphologically defined cell types. Recently, single-cell RNA sequencing approaches deciphered a molecular map of these neurons, attributing specific gene signatures to each one of the 200 phenotypically-defined cell types (11). Furthermore, Özel et al. proved later those specific combinations of terminal selectors expression

could be found in each cell cluster, and that the expression of these genes is sufficient for a cell to engage in a cell-type specific differentiation program (12). In conclusion, cell type differences at the molecular level during development are mostly regulated by transcription factors able to express key identity genes for neurons.

CELL SUBPOPULATIONS: DEFINITION AND IMPORTANCE IN DIFFERENT SYSTEMS

The performance of neuronal circuits is based on the specific connections established between cells that might not necessarily share the same characteristics. Not only may they not share the same cell identity (i.e., glutamatergic and GABAergic neurons coordinated actions inside the same circuit), but also might have subtle and discrete differences within their transcriptomes; for example, the expression or the absence of specific genes, normally referred to as "markers". These marker genes are key for functional cognitive performance, since different cell subpopulations belonging to the same neuronal type are required for cognitive processing, as well as transmission and integration of information (13). Single-cell RNA sequencing is currently the gold standard technique to access these gene expression differences. It has provided a deeper understanding of neuron subpopulations in different brain areas and in different species (7,14). To illustrate the variety of cell subpopulations within the nervous system, cortical interneurons are commonly used as an example. These GABAergic inhibitory cells show a great diversity not only in terms of morphology and physiology, but also in their transcriptional programs. A coordinated action of all of them is needed for the proper functioning of the brain cortex: over 50 subtypes of cortical interneurons have been identified in mice, and they can be classified in subclasses with similar features (15). Parvalbumin-expressing (PV+) interneurons are the largest group and they all share a common fast-spiking firing pattern. Among PV+ interneurons we can find chandelier cells, PV+ basket cells and PV+ translaminar interneurons – although this last subtype is rather rare. Two other main markers are used to classify cortical interneurons: somatostatin (SST) and the serotonin receptor 5HT3a. Subgroups within these subpopulations and their specific markers are described in Table 1.

PV +	Chandelier cells	
	Basket cells	
	Translaminar interneurons	
SST +	Non-Martinotti cells	
	CR+: Martinotti cells	
	NOS+:Long-projecting cells	
5HT3aR +	**VIP +**	**CR+**: Bipolar cells
		CCK+: Basket cells
	NPY+	Neurogliaform cells
		Multipolar cells
		Reelin+: Single bouquet cells
	Meis2+: intersticial cells	

Table 1: Summary of cortical interneurons subtypes according to markers expression. Reviewed at Lim, L. *et al.*, *Neuron* (2018).

When cell subtype is not enough

A similar case can be found in the mammalian cerebellum, where multiple subtypes of molecular layer interneurons and Purkinje cells can be found (16,17) and will be discussed below. In both systems, the different cell subpopulations are embedded in specific circuits to accomplish specific cognitive functions. According to Peter's rule, neurons connect each other by chance, depending only on the apposition of pre- and postsynaptic terminals (2,18). Nevertheless, numerous contradictions to this rule have been described showing that neurons do not wire in a random fashion (19–22). Therefore, there must be a mechanism biasing connectivity towards specific partners regardless of their proximity. It has also been argued that the limited number of genes in the human genome (~ 3·104) cannot be enough to encode the individuality of every synapse in the brain (~ 10^{15}) (4) – a notion already proposed by

Sperry in 1963 (23). Moreover, present understanding of the genome architecture indeed shows that the characteristics of certain protein families would allow a molecular diversity high enough to accomplish this.

SINGLE-CELL IDENTITY: FUNCTIONAL RELEVANCE AND HOW TO ENCODE IT

Certain requisites could be expected from a candidate group of molecules to encode brain connectivity. Firstly, these might be membrane proteins, since they are highly likely to be involved in cell-cell recognition. Secondly, these cell-cell interactions could be either adhesive or repulsive, to promote or discard connections. Therefore, cell adhesion molecules (CAM), are strong candidates to be part of this code. Thirdly, the genes encoding these molecules must be able to provide high isoform diversity which can be achieved from multiple mechanisms, such as the use of alternative promoters, alternative splicing or methylation of DNA. Recent studies have shown an immense variety of CAMs being expressed in the surface of neurons (24). Finally, their expression is expected to be regulated during perinatal development, since it is during this period that neuronal circuits are established and refined (even if plasticity mechanisms may act later in the life of the organism).

cPCDHs in cerebellum Purkinje cells: candidates for connectivity encoders

Purkinje cells are the sole output of the cerebellum cortex and are strongly involved in coordination and motor functions. After birth, each Purkinje cell is contacted at the cell body by multiple climbing fibers (CF) with equal strength. During the first weeks of postnatal development, only one of these CFs is strengthened and translocated to the dendrites at the expense of the "loosing" fibers, which are progressively eliminated to achieve a 1:1 connectivity in the adult brain (25,26). It has been shown that the refinement of this circuit can only be accomplished during this specific time window, referred to as a "developmental critical period". After this time window is closed, CFs cannot be selected or eliminated. Importantly, when Purkinje cells are cultured in the absence of CFs and exposed to them only after the closure of the critical period, CF synapse elimination cannot be achieved. In parallel, when Purkinje cells have already experienced synapse elimination and are exposed to a new set of CFs in culture, mono-innervation is immediately attained (27). These results may indicate that synapse elimination process in Purkinje cells, beyond being activity-dependent, controls long-term recognition mechanisms that allow these cells to select an appropriate presynaptic partner. It may suggest, in turn, that the expression of certain proteins is regulated during CF competition to shape the identity of Purkinje cells and their availability for connection. In this regard, certain CAM families expressed in Purkinje cells have been proposed to mediate the refinement and stabilization of the circuit (24). Among them, cPCDHs seem to be convincing candidates. cPCDHs genes are encoded in the genome in three clusters (alpha, beta and gamma cPCDHs). Each of these clusters contain up to 22 exons whose expression is regulated by alternative promoters. These promoters are also the target of methylation for epigenetic regulation. In Purkinje cell membranes, cPCDHs are assembled as heterotetramers, but trans interaction is strictly homophilic, meaning that only tetramers containing the exact same isoforms will drive cell-cell interaction. Considering the stochastic expression of these alternative exons at the single cell level and the regulatory mechanisms, a total of 3·1010 possible cPCDHs combinations can be virtually expressed in each Purkinje cell (28). This combinatorial calculus, together with other functional studies (29) suggest that cPDCHs may play a role in single-cell identity of Purkinje neurons. Furthermore, recent studies have shown that cPCDHs may bias connectivity of neurons in the cortex (30), indicating a broader role of these molecules in single-cell identity beyond the cerebellum.

Conclusions and outstanding questions

In spite of an increasing interest in single-cell identity, and a higher availability of high throughput techniques that allow access to the finest gene expression differences across cells, there remain a lot of unanswered questions. For instance, after identifying an appropriate candidate to encode single-cell identity, how can the mechanisms regulating its expression be investigated? It is possible that the pattern of expression of these proteins is genetically predefined, as it has been experimentally proven that neuronal circuits can emerge in the absence of neurotransmitter release (5). This may indicate that the encoded neuronal circuits and cell-cell recognition mechanisms that we observe in mammals today are a result of natural selection over thousands of years. On the other hand, it has also been shown that sensory input strongly biases the final connectivity of the brain (6). From a Darwinist point of view, the fact that neuronal circuits remain plastic during development ensures a better adaptation to the environment, a better response to stimuli and thus a better survival of the individual. Considering the experimental proof available, it is likely that the expression of molecules defining single-cell identity is the subject of an interplay between predefined mechanisms and a Hebbian-like regulation that will shape the final version of the circuit. This would mean that there is a selection of efficient neuronal circuits not only at the geological time scale, but also during the development of each individual.

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LETTER

Bridging the gap: 7 misconceptions about brain modelling

Hugo Chateau-Laurent [1,2,3]

[1] Inria Center, University of Bordeaux
[2] Institute of Neurodegenerative Diseases (IMN), University of Bordeaux
[3] LaBRI, University of Bordeaux

Hugo Chateau-Laurent

Born in Nancy (France), Hugo has a Bachelor's Degree in Mathematics and Applied Informatics from the University of Lorraine and a MSc in Artificial Intelligence from Radboud University. He is currently a PhD student at the IMN working under the topic "Bio-inspired strategies for episodic reinforcement learning". Appart from the PhD, he is Co-founder of the Maison de l'Intelligence Naturelle et Artificielle (MINA).

As a PhD student working on brain modelling, I am convinced that experimental and theoretical scientists need to collaborate to get a deeper understanding of the brain. Yet, I often witness difficulties in bridging the gap between these two disciplines. With this letter, I address some misconceptions that experimentalists might have about brain modelling and what we could do about it to bridge the gap.

Misconception 1: Modelling is a recent field

'What I cannot create I do not understand'. These words from Richard Feynman echo in many scientist's minds so much, that capturing biological mechanisms with models has been an approach naturally followed since the early days of neuroscience. Early pioneers like Lapicque (1) or Hodgkin and Huxley (2), proposed models of neural activity that laid the groundwork for modern neuroscience. Models have been around for decades, and computational neuroscience was officially declared a subfield of neuroscience in 1988 (3).

Misconception 2: Modellers manipulate abstract concepts but lack knowledge about the underlying biology

Models are designed to make sense out of complex phenomena and their multi-level interactions using computational tools. In other words, modellers are seeking the best formal analogies to describe how the brain works. A famous saying, we like is 'if the only tool you have is a hammer, it is tempting to treat everything as if it were a nail'. For this reason, modellers should try not to misinterpret biology for the sake of fitting into their theoretical framework. They are in fact expected to be aware of and take into

account recent developments in biology. However, generalists make poor specialists, and close collaboration with experimentalists helps modellers stay up-to-date.

Misconception 3: Models are always missing or simplifying something

As George Box famously wrote, 'all models are wrong, but some are useful'. As stated above, neuroscience models address complex phenomena. Moreover, computer simulations require an exhaustive specification of the components of a model in order to run. That is why all models have limits and a narrow scope, which should be clearly stated. In fact, parsimony is an important quality when it comes to modelling. If a map was to specify the territory exhaustively, it would offer no added value to its reader. Similarly, models should aim to capture the essential features of the system of interest and the laws underlying raw data, in order to have explanatory power. This misconception is very problematic when shared by reviewers with no experience in modelling and unreasonable expectations (4). The documentary in Silico tells the story of how a billion euros were raised for the Human Brain Project, with the aim of simulating the whole brain. The project and its founder Henry Markram were heavily criticized for its unrealistic nature and a new direction was quickly taken.

Misconception 4: Models are too complicated

Models can involve complex mathematical equations, yet their comprehension and application are sometimes intuitive. For example, drift-decision models, a type of model used to describe decision making, are conceptually very simple and have been used to explain a wide range of experimental findings (5), while involving advanced calculus notions.

Misconception 5: Like experimental science, theoretical neuroscience is only descriptive

The term 'model' encompasses a wide variety of tools designed with different aims (6,7). Unlike experiments, these tools can provide more than descriptive explanations. When facing a model, it is important to identify whether it is answering a 'what', a 'how', or a 'why' question (6). A descriptive model (what) of a place cell could describe its place field (i.e. response function) with a mathematical equation. A mechanistic model (how) could show that certain connectivity patterns and intra-neuronal processes lead to place cell dynamics. Finally, a normative model (why) could appeal to the place cells' key role in supporting a navigation system to explain why we can find them in the brain.

Misconception 6: Modellers want to replace experimentalists

Models offer a fantastic playground to test hypotheses directly in silico, and computer simulations have been proposed as candidate replacements for animal experimentation. However, models are only as reliable as the data they are based on, and the best way to improve the accuracy of these models is to provide them with more accurate data. Crucially, certain guidelines should be taken into account in data reports in order to maximize their exploitability by modellers (8). While combining experimentation and computational methods can reduce the number of sacrificed animals, simulations alone will probably not fully replace animal testing.

Misconception 7: Models do not suffer from the replication crisis

As computer simulations are usually deterministic, we could expect computational studies to be highly reproducible. In 2020, the Ten Years Reproducibility Challenge initiated by ReScience C, a journal that publishes replicated computational studies, dared scientists to run their old codes again. Many reasons, including (but not limited to) lost code, dysfunctional hardware, dead languages, or missing documentation, made this quest harder than expected (9). In order to avoid these issues, Benureau and Rougier (10) provide best practices for scientific coding, as Fjola mentioned in the first letter published in BrainStorm.

I hope I have clarified some misunderstandings experimentalists might have on brain modelling. As I wrote this letter, I realized that I was probably guilty of some of the misconceptions myself. Responsibility for miscommunication between experimentalists and modellers is for sure shared by both parties. We modellers probably hold as many, if not more, misconceptions about the work of experimentalists. As proposed by Bower and Koch (8), the solution might reside in experimentalists making models and modellers performing experiments.

DISSEMINATION ARTICLE

A quick journey through autism diagnosis: addressing the difficulties

Simon Lecomte [1]

[1]Interdisciplinary Institute for Neuroscience (IINS), 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 main character of *Rain Man,* Beth Harmon from *The Queen's Gambit*, the great Sheldon Cooper from *The Big Bang Theory*, Woody Allen, or yet Tim Burton: we all have in mind real people or fictional characters who are referred to as autistic – sometimes even without an established diagnosis. It is easy to imagine a set of character traits, behaviours and attitudes that we unconsciously attribute to autism. Despite its presence in our fictions, and more generally in our societies (the prevalence of autism in the world is estimated at 100 cases per 10,000 people) (1), a major problem of diagnosis remains.

The aim of this short article is to explain some of autism causes, which taken as a whole, may shed light on why its diagnosis is still a challenge for neurologists and psychiatrists today.

Let's start by giving a short definition of autism. Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterised by a great heterogeneity of symptoms that can manifest with different intensity, hence the term 'spectrum'. It can include language and learning disorders, difficulties in interacting with the environment (especially the social one), and motor disorders (2). This large spectrum of symptoms has ended in a poorly diagnose, with a lack of genes and biological markers to identify individuals with ASD.

The first difficulty to overcome is that of **co-morbidities**. ASD shares many symptoms with a number of pathologies (3). I will just mention some of them for the sake of conciseness:

- **Attention deficit disorder** shares with autism the difficulties in social interaction, communication, and repetitive behaviours.
- **Dyspraxia** (a developmental coordination disorder) shares with autism some motor troubles.
- **Intellectual disability** shares with autism the difficulties in learning and language acquisition.
- **Anxiety and depression** share with autism the socialisation disorders and more generally a latent anhedonia, consisting of the loss of interest and inability to experience pleasure (4).

The second difficulty is that of **gender bias**. Indeed, even if autism in general is challenging to diagnose, this is even more the case of girls and women (3). Our societies suffer from unconscious, shared and transmitted biases, particularly regarding gender. Girls and women are seen as more shy, reserved, and quiet than boys and men. Since many years, strategies for "camouflaging" symptoms in women with ASD have been studied (5). For example, during adolescence (a crucial period of socialisation) young autistic women use strategies such as imitating non-verbal language (e.g. sustained eye contacts, facial expressions related to emotions) in order to create social relationships. Consequently, because they have internalised the importance of socialisation and its normative aspect, they tend to initiate and develop more friendships than men with ASD.

A third difficulty is that of **socio-cultural disparities**. Depending on the socio-economic level or cultural differences, ASD can be more difficult to diagnose (3). The higher the socio-economic level, the more language and learning problems appear as 'abnormal', and the easier it is to have recourse to medical institutions to make such diagnoses. Besides, depending on the culture, the way of socialising can be diametrically opposed, making it very difficult for a neurologist or psychiatrist from a different culture to establish a diagnosis. For example, in China, direct and prolonged eye contact may be considered rude, people with autism who have been socialised in a Chinese cultural environment will tend to make repeated and sustained eye contact with their interlocutor, which is seen 'normal' in our Western cultures.

This overview of the possible causes that partly explain the difficulty of diagnosing autism is only an introduction and is therefore not exhaustive. Nevertheless, it may raise arguments that are rarely heard and could be important to disseminate more widely. It is crucial today to solve this major problem of diagnosis, not to stigmatise what is now called "neurodiversity" (6). But it should not be forgotten that autism has an actual impact on the lives of people suffering from it and their families. A proper diagnosis is necessary to help them and improve their quality of life.

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Neurometeme

PALM before the STORM

Carmen Guerrero, 2nd year of NeuroBIM master

Editorial board

Khadija Inam

Khadija is a Pakistani student currently pursuing a training as a Clinical Research Associate at the University of Bordeaux. She graduated with a Bachelor's degree in Applied Biosciences from the National University of Sciences and Technology, and later the NeuroBIM Master's degree in Neurosciences from the University of Bordeaux. Her research interests are in the scope of pharmacology and neurological disorders.

Louise Eygret

Born in Gien, France, Louise did her Bachelor's in Life Sciences followed by the NeuroBIM Master's in Neurosciences. Currently, she is pursuing a PhD focused on the neural substrates underlying odor modulation of food intake regulating neuronal circuits. Her research interests are primarily in nutrition, olfaction and hypothalamus.

Juan Garcia-Ruiz

With two Bachelor's degree, in Psychology and Biochemistry, and the NeuroBIM Master's degree in Neurosciences, Juan is now pursuing a PhD where he is focuses on the role of lactate in basal synaptic transmission, which allows him to combine his research interests in biochemistry, electrophysiology and neurometabolics. Although he speaks near-perfect French, Juan comes from Huelva, Spain. He is also the co-founder of neuronhub (www.neuronhub.org).

Sara Carracedo

Sara is a PhD student at the Neurodegénératives Diseases Institute (IMN). She comes from Pontevedra, Spain and holds a Veterinary Bachelor's degree from the University of Santiago de Compostela, Spain and she did the NeuroBIM Master's in Neurosciences. Her PhD is focused on understanding the role of P2X4 receptor in ALS pathogenesis and biomarker in which she is interested in neuroinflammation and receptor trafficking.

Simon Lecomte

Simon is originally from Lyon, France. He did his Bachelor's of Psychology from Strasbourg, after which he did the International Master of Neuroscience from Bordeaux. He is a PhD student studying how the Fragile X Syndrome impacts the presynaptic mechanisms at the DG-CA3 synapses from which one can guess that his interests lie in memory, synaptic communication and the hippocampus. He also runs a blog "Astrocytes et traumatismes crâniens juvéniles".

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