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In this issue

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BRAINSTORM STUDENT JOURNAL

REVIEW

Pain processing in cortical areas

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Born in Bordeaux (France), Thibault holds a Bachelor's degree on Biology and a master in Neurosciences from the University of Bordeaux. He is currently third year PhD student at the IMN where he is interested on the neuroanatomical basis for the anti-nociceptive role of RLN3/RXFP3 peptidergic system. His research interests include neural circuits, neurophysiology and computation. He has a personal project on Instagram called @no_brainerdd where he shares neurosciences images with the Instagram community.

Abstract

Chronic pain is a major burden with a very high prevalence worldwide. In order to find efficient treatments, many studies focus on cortical regions involved in different dimensions of pain processing. In this review we will describe how the anterior cingulate and somatosensory cortices are implicated in cognitive, emotional, and sensory-discriminative aspects of pain, respectively. We will also examine possible therapeutics strategies to treat psychiatric disorders associated to chronic pain.

Keywords

Analgesia, chronic pain, cingulate cortex, nociception, psychiatric disorders, and somatosensory system.

Abbreviations

ACC: Anterior cingulate cortex

CFA: Complete Freund Adjuvant

CNO: Clozapine n-oxide

DRG: Dorsal root ganglia

S1: Primary somatosensory cortex

S2: Secondary somatosensory cortex

SSC: Somatosensory cortex

MEG: magnetoencephalography

PAG: Periaqueductal gray matter

ACC: anterior cingulate cortex

PV: Parvalbumin

SNI: Spared nerve injury

SOM: Somatostatin

Introduction

Affecting more than 25% of the world population (1), chronic pain is a major health issue. Pain is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (IASP, 2020).

The physiological mechanism that processes noxious stimuli is nociception. The nociceptors convert external stimuli into molecular signals that ensure the transmission of nociceptive information to the brain (2). The terminals of nociceptive fibers are specialized in the detection of different stimuli (like thermal, mechanical, and chemical) and are triggered only by high intensity stimuli susceptible to induce damage of any kind.

The response of the organism to those noxious stimuli is proportional to the intensity of the stimulation. Located in dorsal root ganglia (DRG) (4), the cell bodies of nociceptive fibers innervate the dorsal horn of the spinal cord (2, 5). Then, superficial and deep laminae of the dorsal horn are the first relay for pain signal (5) before projecting to brain structures through ascending pathways, including cortical areas considered as part of the “pain matrix” (6).

On the one hand, the processing of pain signal processes of pain signal in extra-cortical structures have been the subject of intense research, especially in the spinal cord (7, 8, 9, 10, 11). On the other hand, the study of brain regions involved in pain integration is important to describe the three components of pain: sensorial, affective and cognitive (12, 13, 14, 15). First, the sensory dimension identifies the nature of the noxious stimuli and defines their location and intensity. Second, the affective dimension determines the emotions that accompany pain and depends on each individual’s experiences. The cognitive dimension includes the memory, perception and evaluation of the pain (13). To date, these three dimensions are still under debate, especially with regard to their definition and the description of their main features (12, 14, 15).

Pain as an acute response to a harmful stimulus is a vital mechanism to keep the integrity of our organism. The peripheral or central sensitization driven by nociceptive mechanisms usually diminishes progressively after the injury. However, when pain is too long lasting (more than 3 months in humans), it may become chronic and is accompanied by hyperalgesia (increased response to painful stimuli) and allodynia (decrease of pain threshold). The chronicity transforms pain into a highly disabling pathology, further worsened by the high prevalence of psychiatric comorbidities. Indeed,85% of chronic pain patients also face stress, anxiety and/or depression (17, 18, 19). Unfortunately, there are currently no satisfactory treatments for patients suffering from this condition (20).

The goal of this review is to provide an overview on pain integration and modulation in cortical areas with a focus on two different regions: the somatosensory cortex (SSC) and the anterior cingulate cortex (ACC).

Methods

Review editing

The different articles cited in this review have been found through PubMed and Google Scholar using the following keywords: pain, chronic, interneurons, cortical areas, anterior cingulate cortex, somatosensory cortex, analgesia, anti-nociceptive, nociception, anxiolytic, depression.

Models to study chronic pain

The origin of chronic pain is diverse and characterizes 3 main pain subtypes:

1. Inflammatory pain appears after tissue damage resulting in the liberation of immune cells and inflammatory mediators (21 ,22 ,23).

2. Neuropathic pain arises from an injury of the nervous system, be it peripheric or central (6, 21).

3. Nociplastic pain is described as a

dysfunction in pain processing, with patients reporting pain despite the absence of damage to the organism (24).

To study inflammatory and neuropathic pain different animal models have been developed in order to reproduce allodynia and hyperalgesia observed in chronic pain. Inflammatory pain models can be induced through the injection of Complete Freund Adjuvant (CFA) in the hind paw or collagen in the knee joint of the animal. Neuropathic pain model can be induced through chemotherapy or obtained after lesion of peripheral nerves (e.g. spared nerve injury, SNI; nerve constriction protocol, cuff). Mechanical and thermal sensitivity are assessed respectively with the von Frey test (by using monofilaments as punctate stimuli and applying different intensities) and the plantar test (by using an infrared stimulation as thermal stimulation) in which withdrawal threshold can be measured.

Results

Role of prefrontal and somatosensory cortex in pain perception

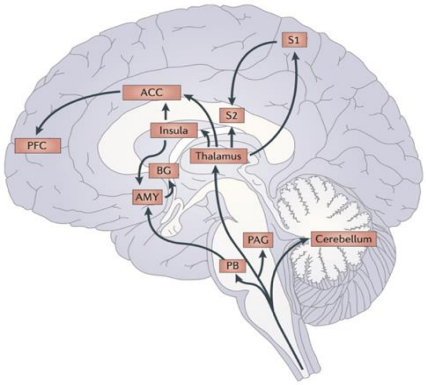

Figure 1: Afferents ascending pathways to the pain matrix. Ascending pathways initiating from dorsal horn of the spinal cord are projecting to cortical structures. The spino-parabrachial tract, making a relay in the brainstem before projecting to amygdala (AMY), insula, and cingulate cortex (ACC) involved in affective and cognitive dimensions of pain. The lateral spinothalamic tract, making a relay in lateral thalamus, projecting to somatosensory cortex (S1/S2) and involved in sensory dimension of pain. BG (Basal ganglia); PAG (Periaqueducal grey matter), PB (Parabrachial nucleus), PFC (Prefrontal cortex). From Bushnell et al. (2013).

Anterior cingulate cortex

The ACC is a key cognitive structure important for memory, anticipation or decision-making processes (25, 26, 27). An optogenetic approach performed in this region showed that specific activation of glutamatergic inputs to periaqueductal gray matter (PAG) induces an increase in pain avoidance behavior (28). Evidence suggests also that the ACC is playing a major role in memory related to pain. Specific knock-out of calcium channel Cav1.2, central in ACC excitability, showed a decrease in freezing after a painful stimulus (29).

The ACC, by its connections to the amygdala (30), is also known as an important area for the affective component of pain (27, 31). Study of cerebral blood flow and glucose metabolism showed an increase of ACC activity in patients presenting anxiety symptoms (32). Recordings of evoked glutamatergic postsynaptic currents in pyramidal cells of the superficial layers of the ACC exhibit strong plasticity events at the synapse. Cortical presynaptic long-term potentiation (pre-LTP) induces an increase of psychiatric symptoms related to chronic pain (33). In addition, optogenetic activation of pyramidal neurons of the cingulate increased significantly anxiodepressive-like behaviors (34).

Although ACC is described as a region implicated in different pain components (22, 27) (Fig.1) its subregions seem to have more distinct functions. In a study focusing on rostral anterior cingulate cortex (rACC), the specific lesion of this region displays its role in emotional dimension of pain. The lesion made by ibotenic acid injection induced a decrease of aversive behavior, while sensory-discriminative behavior seems not to be affected as paw withdrawal threshold levels remain unchanged (35).

Somatosensory cortex

A recent study reports data obtained with whole-head magnetoencephalography (MEG) in human revealed very specific temporal patterns of activation. Results showed that the activation of primary (S1) and secondary (S2) somatosensory cortex is simultaneous and contralateral to the side where the harmful stimulus is presented. Moreover, pain processing by ipsilateral S2 happened after contralateral side (36). In the S1, recent evidence suggests a spatial distinction in

pain processing. Neurons of S1 granular region are more selectively activated by a noxious stimulus, meanwhile neurons of the dysgranular region are important for tactile sensation and initiation of pain-like behavior. However, in pathological conditions such as neuropathic pain, the nociceptive role shiftes from granular neurons to dysgranular neurons (37).

In neuropathic pain condition, the activity of the primary somatosensory cortex (S1) is impacted. The activity of glutamatergic neurons from layer 5 of the S1 is upregulated in SNI condition as compared to healthy animals, through the increase of dendritic Ca2+ spikes (38).

Therapeutic perspectives to treat chronic pain

Nociception impairments

Different strategies have been considered over the years to reduce nociception impairments in chronic pain. In the ACC, several results suggest that targeting descending pathways can be a good way to alleviate pain sensation (35, 39). The restoration of local inhibitory activity by cell transplant in the ACC also induces pain relief through decrease of pyramidal neurons activity in a neuropathic pain model (Fig.2A/B) (35). In a recent study, specific activation of GABAergic parvalbumin (PV) - expressing interneurons with an optogenetic approach has been performed to inhibit pyramidal neighboring cells in inflammatory pain conditions (Fig.2C/D). The results obtained show that inhibition of glutamatergic activity induces an increase in paw withdrawal threshold indicating an analgesic effect (39).

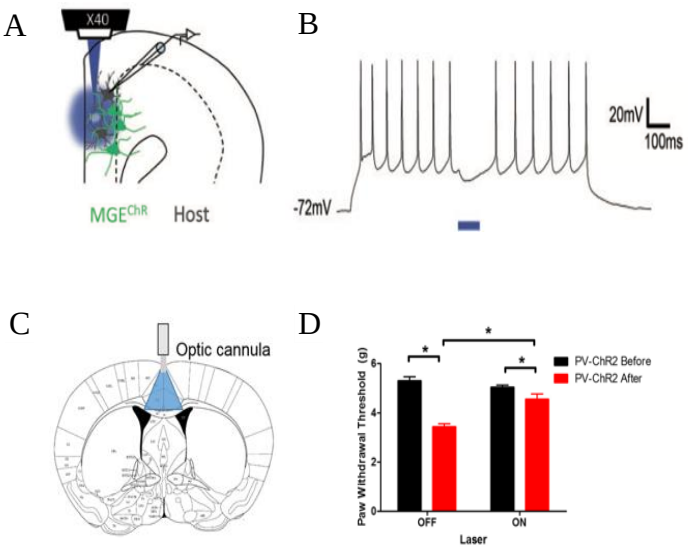

Figure 2: Effects of inhibition of ACC glutamatergic activity on nociception. (A) Optogenetic activation of GABAergic cell transplants (MGE) in the ACC. (B) Activation of MGE results in blocking of pyramidal neurons firing responsible of allodynia (from Salinas et al., 2019). (C) Optogenetic activation of GABAergic PV-interneurons in ACC of PV-Cre mice. (D) Activation of PV-positive interneurons induced a decrease of mechanical threshold in inflammatory pain condition (CFA) (from Kang et al. 2015).

In the S1, the activation of somatostatin (SOM)-expressing GABAergic interneurons induces downregulation of pyramidal neurons hyperexcitability (38, 40). The specific activation of SOM interneurons has been done with a chemogenetic protocol and CNO (clozapine n-oxide) injection in SOM-Cre mice.

Therefore, the mechanical allodynia resulting from neuropathic pain is prevented after glutamatergic activity decrease in the SCC (Fig.3A/B) (38).

Together, the results gathered in the ACC and the SSC emphasize the role of inhibitory neurons as key regulators of nociception, but also as important therapeutic targets to treat chronic pain.

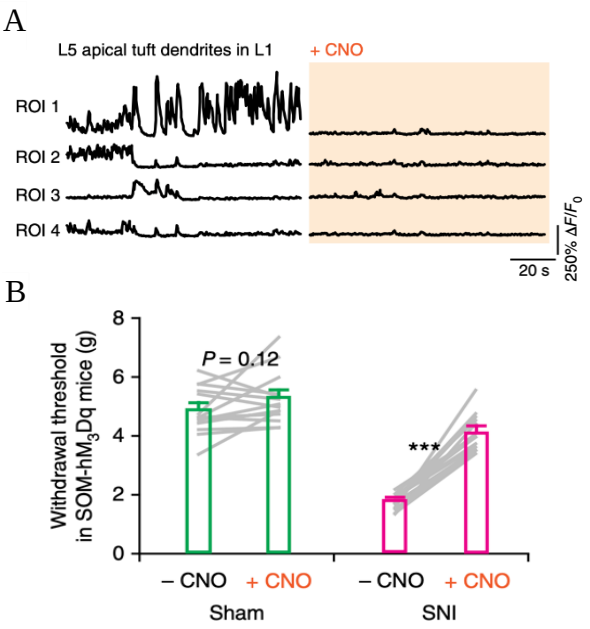

Figure 3: Effects of SSC glutamatergic inhibition on nociception. (A) Chemogenetic activation of GABAergic SOM-expressing interneurons in S1 induced a decreased in pyramidal neurons activity. (B) Acute activation of SOM-positive cells through CNO results in increase of paw withdrawal threshold in neuropathic condition with no effect on basal mechanical sensitivity (from Cichon et al., 2018).

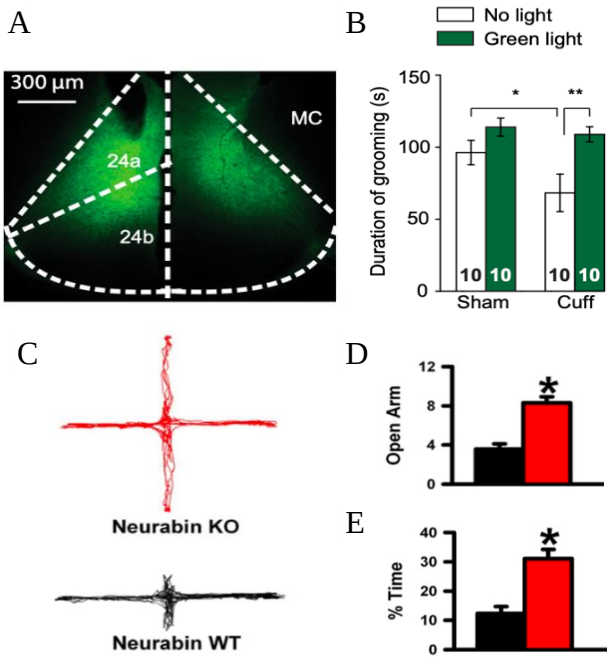

Figure 4: Effects of ACC glutamatergic inhibition on anxiodepressive-like behaviors in neuropathic pain condition. (A) Expression of CaMKIIa-ArchT-EYFP in transfected cells of the ACC. (B) Optogenetic inhibition in ACC results in an increase of grooming duration reflecting a decrease of anxiety phenotype (from Sellmeijer et al., 2018). (C) Traces of mouse movement in the elevated plus maze. (D) Number of entries in open arms. (E) Time spent in open arms (from Kim et al., 2011).

Psychiatric comorbidities

Modulation of excitatory outputs of the ACC by GABAergic interneurons is also a target for the treatment of pain-related comorbidities, such as anxiety-like behavior (41). Similarly, inhibition of ACC pyramidal neurons via optogenetics in a neuropathic pain model induced the extinction of anxiodepressive-like behavior observed with the splash and novelty suppressed feeding tests that are expressed in ACC neurons has been proved to be efficient against anxiety in neuropathic pain condition. Indeed, selective inhibition of neurabin mRNA with siRNA has positive effects on anxiety phenotypes (Fig.4C/D/E). Mice are presenting an aversiveness to open space, thus the time spent in the open arm of the elevated plus maze is a marker for anxiety (43).

Conclusion

Overall, in addition to dorsal horn of the spinal cord, the function of cortical areas for pain integration is central. Evidences show the role of ACC in the cognitive component of pain, with different studies indicating that ACC inhibition causes pain-induced dysfunction in decision-making or learning. In addition, lesions of this area result in the emergence of anxiodepressive symptoms highlighting the role of the ACC in emotion regulation. Concerning the SSC, study performed in S1 and S2 subregions display its complex role in the discrimination of pain sensation.

Different studies suggest that inhibition of glutamatergic activity is an interesting therapeutic target for the treatment of nociceptive impairments related to chronic pain. In both the ACC and SCC, anti-nociceptive effects have been observed after inhibition of glutamatergic pyramidal cells by GABAergic

interneurons. However, evidence suggests that inhibition is mediated by different subtypes of GABAergic cells, through SOM-positive interneurons in the SSC and PV interneurons in the ACC. In addition, the decrease of glutamatergic activity in the ACC seemed very efficient against anxiety and depressive symptoms.

In conclusion, the modulation of glutamatergic activity in both ACC and SCC can be considered as a promising possibility in the treatment of nociceptive and psychiatric comorbidities appearing in chronic pain condition.

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BRAINSTORM STUDENT JOURNAL

LETTER

Criminal Psychology- Looking through a keyhole

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A topic that has found itself more and more frequently at the heart of debate in recent years, a subject of documentaries like 'Conversations with a Killer: The Ted Bundy Tapes' and TV shows like 'Mind Hunter', Criminal Psychology attempts to offer a glimpse (often an unpleasant one) into the depths of the criminal mind in order to understand what could possibly drive an otherwise common man to break down the moral and ethical barriers that prevent them from inflicting harm, whether it is material, physical, spiritual, financial, mental or emotional.

The discourse that revolves around what motivates criminal behavior is largely led by behavioral scientists keen on untangling the complex mesh of all the intrinsic and external factors that could cause it. This, of course, rests on the idea that such an understanding could pave a way for prediction, and consequently prevention, of crime, as well as the creation of intervention and rehabilitation strategies for criminals —by extension reducing the risk of a recurrence of delinquent behavior.

For the sake of brevity, this letter will discuss only some important theories in criminology and also how criminal psychology is factored into the legal justice system. To not digress and delve too deep into the subject, we will dismiss the notion of innate evil and the notion that one's conscious mind could be acutely aware of the implications of one's actions and proceed nonetheless (otherwise known as the choice theory in criminology). Importantly, this letter will consider crimes that are universally agreed upon and will not account for criminal acts that stem from survival instincts, and/or due to an absence of alternative courses of action.

To begin, of the numerous criminology theories that exist to present date, perhaps the most known are those extracted from the works of Sigmund Freud, an Austrian psychoanalyst largely recognized as one of the first contributors to the field of clinical psychology. One of Freud's notable theories is his structural theory of personality which describes the complexity of the human personality by breaking it down into three components: the id, the ego and the superego.

The id, an unconscious element, comprises of the primal, biological, human instincts and reflexes driven by personal pleasure, needs, desires, and coupled with the urge to indulge all such impulses immediately. This is the selfish element that does not consider rationale, reason or morality. The ego, a conscious, subconscious, and unconscious element, functions to satisfy the id whenever possible, but in a more logical manner, through delayed gratification, compromise, or rejection – through a balance of pleasure and pain, benefit and risk. The third element, the superego, a conscious and unconscious element, is the only one of the three that considers right and wrong before action. The superego is an interesting concept that has two essential parts: the conscious and the ego ideal, 'the ideal self'. Conscious, perhaps self-explanatory, prevents one to act on morally questionably behaviors, while the

ego ideal applies on the self the benchmarks of good and acceptable behaviors to achieve. Branching from this concept of ego ideal is the Freudian concept of 'guilt' – when an individual is unable to satisfy (or meet the standards of) the ego ideal.

Freud, in his theory, explains how these three components interact to give rise to human behavior, with the ego and superego regulating for the id to be satisfied in not only a realistic manner, but also a morally acceptable one. According to Freud, the conflict of the id, ego and superego shape personality and behavior, and that criminal behavior is essentially a failure of one element: the superego.

Importantly, this theory is intertwined with Freud's theory of the stages of psychosexual development which discusses how the interaction of these three elements is altered and influenced from childhood to adulthood. Throughout these stages, conflict is assumed to arise between these three elements, the result of which alters personality and behavior. Freudian theorist believe that conflict leading to behavioral problems, such as: selfishness, aggression, impulsiveness, lack of guilt and empathy during the stages of development described by Freud would prevent the development of a sound sense of right and wrong. His theory also furthers the notion that mental issues, notably those stemming from complicated childhood experiences, would, therefore, increase the chances of criminal behavior in affected individuals.

Of course, Freud was bold for his time, and his theories remain controversial even amid modern-day psychoanalysts of criminal behavior; however, his theory did open doors to conversation around how childhood, upbringing and social factors would affect adult behavior from a moral point of view. Theories like Social Learning Theory (which explains how behavior of other individuals in one's social environment sets the tone for what is and what is not morally acceptable), Social Disorganization Theory (which states that people living in areas of high crime-rate would develop a more lenient moral perspective than if they had been living in low-crime rate areas) and Life Course Theory (which suggests that the events occurring in a person's life at different stages can lead the person to a point where one triggering event causes them to morally falter and commit crime) resonate with Freudian concepts.

Now, this letter has mentioned behavior 12 times already, so let's look at how it factors in. Behavior essentially originates from the brain, which is why understanding criminal behavior draws attention to investigating the neural play at work. Since complex behavior does not follow a single, principle pathway, it becomes trickier to understand and pinpoint the neural disruptions in a behavioral circuit that would illicit morally questionable actions. Imaging methods like fMRI, voxel-based morphometry and PET scan have allowed researchers to identify brain regions implied in moral thinking, and to discover that these are areas associated with emotion and cognition in general. Trauma to these regions have been found to result in morally erratic behavior in individuals; however, there remains a lack of evidence for the existence of a moral cognition with neuronal substrates specific for it —meaning that morality remains as intangible a concept as ever. In fairness, moral decision-making is a complex process and to fully understand it from a neural perspective, researchers would have to take into consideration the heterogeneity of individuals as a result of: genetics, culture, ethnicity, social environment, economic status and geography.

Crimes of violent nature do not occur solely due to a lack of moral awareness. Individuals with mental illnesses (such as schizophrenia) are prone to exhibit aggressive behavior, which is suggested to arise from a combination of neuropathological factors and psychotic symptomatology. This has more to do with neuropsychological and cognitive impairments than anything else, which is why criminal psychologists are needed to evaluate the mental state of a person, particularly in cases of violent crimes.

Not only does criminal psychology provide insights into a criminal's psyche, but also holds an influence in the legal justice system. Intent, motive and act are at major play when it comes to accountability, and depending on how one weighs over the other, a sentence could be negligible, mild or major. On account of very serious criminal offenses, forensic psychologists (or criminal psychologists) are usually brought in to evaluate the mentality of perpetrators to provide more context and ground for the legal team to work with, allowing also for a more informed decision-making process. Such an evaluation thoroughly explores an individual's experiences –their childhood and upbringing, interactions and personal experiences, social and environmental influences, physical and mental health, age, habits, and personality traits to list some areas on interest. People have avoided facing prison for criminal offences on several occasions on the basis of 'not being of sound mind', which may not be frequent especially if there is evidence of 'planning' before the crime, but is not unprecedented either.

The applications of criminal psychology may not be so obvious, but can hardly be dismissed. On numerous accounts, criminal profiling has led to the apprehension of the culprit by way of prediction. In other instances, offenders having gone through adapted rehabilitation and intervention have overcome their internal conflicts to eventually reintegrate into society as members, and not threats. These are two of the many applications, and the rest will remain up to you to find. No doubt, this letter reads like a fleeting glance through a keyhole into a room full of questions on the subject, but if this has stirred a formerly absent curiosity in you, then it has done its job.

DISSEMINATION ARTICLE

What is Huntington's disease?

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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.

This article was reviewed by Jakob Scharnholz.

In 1775, a tropical cyclone wiped out 90% of the population of Pingelap Island. Only about 20 people survived. Among the survivors was the leader of the island, who was also a carrier of a rare genetic disease known as achromatopsia. This disease forced him to see the world in black and white. The leader turned out to be one of the most ardent participants in the biggest project of the island: its repopulation. Why do we know this? Well, 10% of today's Pingelap population shares something with the leader: they inherited his monochromatic vision. This phenomenon is the result of something known as the **founder effect**, an interesting evolutionary concept that can explain the appearance of unusual characteristics in cases where a small group of individuals from a larger heterogeneous community gives rise to a new population.

Pingelap atoll

A century later, on the same continent, another curious case of founder effect took place. An American physician named **George Huntington** described the symptoms of a condition observed in a family of English descent and named the neurodegenerative disease after himself. The first cases are believed to have occurred in Northern Europe, and given the hereditary nature of the disease it spread rapidly, especially in America. The largest known population affected by the disease is in the Venezuelan state of Zulia. The first inhabitants arrived in the early nineteenth century, and because they were so few in number and there were some affected, over time the genetic disease grew in parallel with the population.

What is Huntington's disease?

Huntington's disease is an inherited neurodegenerative disease characterized by motor, cognitive and emotional symptoms. It is a genetic disease triggered by a mutation on chromosome 4. Early manifestations of the disease appear around 35-40 years of age, and include unwanted limb movements (also known as choreic movements) that may make walking difficult, as well as involuntary facial movements. Motor issues are accompanied by cognitive problems such as difficulty concentrating and making decisions. Irritability and depression are common in the early stages. As the disease progresses, opposing symptoms such as slowness of movement or bradykinesia, muscle stiffness and balance problems appear. Regarding cognition, advanced stages of Huntington's disease are characterized by a slowness in information processing, a lack of awareness of the disease itself (a symptom known as anosognosia) and an inability to perform two simple actions at the same time. Patients also show signs of apathy, depression and impulsivity.

Huntington's disease in numbers

The incidence of Huntington's disease is 0.38 per 100,000 people per year. Applied to the French population (64,756,584 people) this amounts to 246 new cases each year. Life expectancy after diagnosis is 10 to 20 years. According to a compilation of meta-analyses by Pringsheim et al. (2012), the prevalence of Huntington's (i.e. the number of cases stable over time, taking into account that it is a disease with a limited life expectancy) is 2.71 affected per 100,000 people.

Biology of Huntington's disease

Huntington's disease is characterized by the **abnormal repetition (36 times or more) of a DNA sequence located on chromosome 4**. This mutation occurs in the gene encoding the huntingtin protein, and results in an abnormal version of the protein that is associated with the appearance of the symptoms described above (although it is not entirely clear how). It is an **autosomal dominant disease.** What does this mean? Our genetic material is composed of 23 pairs of chromosomes: 22 pairs of autosomes and one pair of sex chromosomes that determine, among other characteristics, sex. Chromosome 4 on which the characteristic Huntington's mutation is located is an autosome (that explains the *autosomal* part of the disease). Each pair is composed of a paternal and a maternal copy. That is to say, each parent endows us with one of its two versions of each chromosome. Thus, if the mutation is found in one of the chromosomes of one of the ancestors (as is usually the case), there is a fifty percent probability that an offspring will receive it. Some diseases require the presence of two versions of the mutation (each coming from one of the ancestors). As for Huntington's disease this is not the case: the presence of the mutation in one of the chromosomes is sufficient for the disease to develop. This is referred to as a *dominant* genetic disease.

Neurodegeneration takes place mainly in the cortex and structures belonging to the cortico – basal ganglia loop, such as the caudate nucleus and putamen. These are brain regions related to voluntary movement. The caudate nucleus and putamen are part of the dorsal striatum, and play an important role in the inhibition of movement. This may explain some of the main symptoms of the disease such as choreic movements. Indeed, the decrease in the cells responsible for inhibiting movement, could be at the origin of the emergence of involuntary motor activity. These choreic movements cannot be voluntarily inhibited, but fortunately they cease during sleeping hours.

Neuronal death is probably due to protein aggregation of the aberrant version of huntingtin. The brain structures affected in Huntington's disease are also characterized by disturbed neurotransmitter activity (i.e. the activity of the molecules responsible for establishing communication between neurons is impaired). Specifically, GABAergic and acetylcholinergic activity is decreased, while dopaminergic activity is increased. However, DNA sequence repeats not only affect huntingtin, but are also related to problems in DNA replication (the process by which the cell generates an identical copy of the DNA so that each daughter cell receives a copy after cell division). Indeed, the protein responsible for synthesizing the DNA copy from the DNA sequence that serves as its template can lose its thread and create more repeats than it originally had. In other words, as the disease is inherited, the number of repeats may increase in the offspring. This in turn has an effect on the appearance of symptoms due to the anticipation effect: each new generation that inherits the mutation shows signs at earlier stages. This phenomenon of repeat expansion occurs mostly in male sex cells and is therefore more frequently observed in cases where the paternal ancestor has the mutation. The genetic test that allows predicting the appearance or diagnosing Huntington's disease consists of counting the number of repeats, since it correlates with the appearance of symptoms.

Take home message

Huntington's disease is a neurodegenerative disease with an important genetic component. Neuronal death occurs in the dorsal striatum, a structure involved in the regulation of voluntary movement. One molecular component that could be involved in cell degeneration is huntingtin, the mutant protein that results from huntington's characteristic genetic mutation: abnormal number of repeats of a DNA sequence. It is not yet clear how huntingtin causes neuronal death, but one hypothesis is that the protein resulting from the mutation has components that can interact in a cognate manner and form protein aggregates. Such aggregates are toxic to cells and could induce neurodegeneration.

INTERVIEW

The third element of the brain

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This interview was extracted from the website www.neuronhub.org founded by one of the members of the Editorial Board of BrainStorm (Juan Garcia-Ruiz).

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.

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I am going to tell you a Spanish story of heartbreak. Once upon a time there was a brain ruled by an astrocyte and a neuron. Wait, wait, don't close the article and stick with me for a bit, it's getting interesting. The neuron was the center of attention, it was in charge of the communication between the different parts of the brain and between the brain and the rest of the organs. Thanks to the neuron there was movement, senses, consciousness and memory. The astrocyte was happy feeding the neuron, limiting the entry of intruders into the brain through the blood by forming a barrier (the blood-brain barrier), and it also had a say in communication. They were happy together, complemented each other and even depended a little on each other. Or so they wanted to make us think. A handsome young man named Ramón y Cajal, who was a private detective hired by the little astrocyte, appeared on the scene. Day after day he meticulously observed the brain. But there was nothing new under the sun. Here there was the neuron, over there was the astrocyte. Everything seemed in order. Wait a minute… It turns out there's someone else! There's a third one! That's what he literally called it. "The third element." The little astrocyte was shattered. There always has to be a third party! A little later, Cajal's student named Pío del Río Hortega took over and devoted himself to a very close study of this third element, which he eventually called microglia. And so much for the romantic drama. Now let's talk about serious (and much more interesting) things. Microglia, who are you?

Microglia speaking: I am a multifaceted cell, much better than the astrocyte. I am a doctor, and in my spare time I am a security guard. I keep an eye out for trouble, visit every nook and cranny of the brain looking for intruders with my many arms, and contact neurons to see how they are doing. When I detect a stranger, I literally eat it (function: phagocytosis). Other times I keep some of his clothes and show them to a friend who doesn't mess around so he can identify and take care of him: the T-cell (function: antigen

presentation). But I can also call other friends like leukocytes to come help me where there is trouble (function: pro-inflammation). I can also send everyone home when the battle is over (function: anti-inflammation). Wait, what do you mean? Are you saying that I am not unique and this can also be done by macrophages? Yes, but I can act much faster and I am more effective in getting to the right place (better spatio-temporal regulation). And contrary to macrophages, I don't need to be constantly replaced. Since I am privileged to be in the brain, the organism cannot afford to send new microglia constantly, because the blood-brain barrier is quite selective with who gets through and who doesn't. So I am able to maintain my status quo and proliferate locally when necessary. I also help neurons choose their friends. When I see that the communication between two neurons is no longer what it used to be, I put an end to it (function: synapse stripping). In short, I am there to watch over the health of the neurons when things go wrong, and when things go a little better, I make sure that it stays that way (function: homeostasis). But I'll stop talking about me. I leave you with Agnès Nadjar, who has been very interested in my life and my role in obesity.

Agnès Nadjar is a neurosciences professor at the University of Bordeaux and is interested in studying the effect of nutrition on the brain in the context of obesity. She focuses on microglia, the immune cell of the brain. Agnes did her thesis in Professor Robert Dantzer's lab on the interactions between the immune system and the central nervous system, which sparked her passion for microglia. She did a postdoc on the process of pathological neuroinflammation in Parkinson's disease, and then she was recruited as an university lecturer and researcher in Bordeaux. She also set up a project with Philip Haydon at Tufts University (Boston) on the role of interactions between microglia and astrocytes in the sleep response to inflammation. When she returned to Bordeaux she joined the NutriNeuro laboratory to add a nutritional component to her neuroimmunology studies. Last year she joined the Magendie neurocenter where she is working mainly on obesity and neuroinflammation.

JGR: What are the main dangers of obesity on our health?

AN: Obesity is a major risk factor for diabetes, cardiovascular disease, neurodegenerative diseases, depression and certain cognitive deficits. Moreover, obesity is often accompanied by a decrease in physical activity and apathy. So it is both a physical and a psychological problem.

JGR: Obesity has reached epidemic levels. Between 1995 and 2000 we went from 200 million obese people to 300 million. What do you think caused this increase?

AN: It can be considered a pandemic. It is estimated that 30% of the world's population is overweight and 15 to 20% obese. Why is this? There are several things. First, there was a major nutritional shift a little less than a hundred years ago with the consumption of refined sugar, one of the most obesogenic nutrients. There is also the emergence of the western diet: fast food, pizza, sugary drinks. Associated with this, there has been an increase in sedentary lifestyle. People do less sport and walk less during the day. So overall we move less and we eat bad food in large quantities and at any moment of the day.

JGR: You study obesity on a much smaller scale: cellular and molecular. First of all, what is microglia?

AN: Microglia is the immune cell of the brain. Its role is to maintain an optimal environment for neurons by detecting normal and abnormal variations in the brain and responding to them. This cell is particularly sensitive to nutritional variations and can detect very small changes thanks to the extensions it has around the cell soma. Depending on what it senses, it modulates its activity to protect the neurons and keep them in good shape. The problem is that sometimes the attacks they undergo are too strong and they can no longer protect the neurons.

JGR: How is microglia related to obesity?

AN: Obesity is certainly a disease of the brain rather than a disease of the body. When you look at the susceptibility genes for obesity, they are all linked to brain processes. One of the first things that happens when you eat too much fat and too much sugar is inflammatory activation in the brain produced by microglia. We saw that if we could prevent this microglial inflammatory activation, we could prevent weight gain in animals (to be confirmed in humans).

JGR: In addition to microglia, you've been quite interested in omega-3. What is its role in this context?

AN: Omega-3 is a protective lipid that can prevent microglial inflammatory activity, so it's pretty good for the brain. The problem with obesogenic diets is that there is a major deficit of omega-3s and they contain bad fatty acids and carbohydrates, so the microglia will combine all this information and will lead to inflammation. The Mediterranean diet is quite good in this sense, because it contains vegetables, fruits, olive oil and fish. It has very little saturated fatty acids and it contains omega-3.

JGR: What does omega-3 do in our cells?

AN: The omegas are incorporated into the phospholipids that make up the plasma membranes of every cell in the body. Most of the omega-3 goes to the brain, which is a real pump for this lipid. There is a theory that proposes that the brain of homo sapiens sapiens is what it is since we started eating omega-3 (fish, seafood, etc.). These omega-3s helped build the membranes of the brain cells and they may have roles related to their fluidity and the mobility of the receptors. But these molecules can also be cleaved from the membrane and become molecular signals in the cell, controlling different signaling pathways.

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

AN: The last paper we published that I'm particularly proud of was on the role of omega-3s in brain development. In particular, we studied the effect of a lack of omega-3, which is the case for almost the entire world population. We have seen that when there is very little omega-3 during development, the brain will not develop very well. For example, there will be fewer synapses. Why is this? If the microglia detects this lack of omega-3 it will set up an activity that is detrimental to the synapses. I mentioned earlier that omega-3 can leave the membranes and act as molecular signals. When omega-3s are missing in microglia, they are cleaved and the resulting lipid fragment will activate a cascade of events in the cell and will lead to phagocytosis at the synaptic level. These omega-3s will be missing in the microglia and in the neuron, but what triggers phagocytosis is really the absence of this lipid in the microglia. The consequence is that the neurons end up with less ability to connect with their neighbors and these animals show cognitive deficits when they grow up.

JGR: Do you have any scientific reading to recommend?

AN: When I chose to do my thesis with Robert Dantzer it was because I had read his book The psychosomatic delusion. I thought it was great, the fact that our behavior could be controlled by our immune system and vice versa.

JGR: Any final message for readers?

AN: Never listen to the doomsayers, the people who tell you that you're not going to make it. You just have to do things, you have to go for it when you have a passion!

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Neurometeme:

Simon Lecomte, 3nd year PhD student at the IINS

Announcements

Award: Best Review Article of the Year!

Title: Cellular substrate for predictive processing in cortical circuits

Author: Jakob Scharnholz

Published in Brainstorm: 4th Issue (April 2023)

We are thrilled to announce that Jakob Scharnholz has been the selected winner of the "Best Review Article of 2022-2023" award, a recognition that comes with a cash prize of 100 Euros!

This award celebrates the exceptional contribution of our authors to the field of neuroscience through their insightful and thought-provoking review articles. The winning article was selected based on its relevance, originality, and impact on the neuroscience community.

Review articles are the backbone of scientific discourse, providing in-depth insights and critical analysis of existing research. They serve as invaluable resources for students, researchers, and enthusiasts alike, making this award a testament to the author's valuable contribution to the field. This award is a reminder of the immense potential within the Brainstorm community, and we look forward to more groundbreaking contributions in the future. Thank you for being a part of our journey to make neuroscience accessible and inspiring. Warmest congratulations to our award-winning author!

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Editorial board

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 and 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 neuroimmune interactions 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".

Ludovica Congiu

Ludovica is an Italian researcher hailing from the beautiful island of Sardinia. After getting a master's degree in Neuropsychobiology at the University of Cagliari, she successful pursuit of a Ph.D. in neuroscience at the Universität Klinikum Eppendorf (UKE), in Hamburg. The project was focused on the characterization of the role of the cell adhesion molecule L1 in affecting mitochondrial activity and metabolism. Currently, she's working as an Assistant Ingénieur at the IMN, where she is investigating the role of P2X4 receptors in ALS and anxiety disorders.

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.

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Are you a MSc or a PhD student in neuroscience? Then you are more than welcome to participate in our journal.

You can write either a short-review on a topic of your choice, or a one-page letter (a reflection, a project or an insight you would like to share with the scientific community), a dissemination article about clinical neuroscience (neurodegeneration, neurodevelopmental or psychiatric disorders…) with the aim to reach a more general public, or a neurojoke.

Don't start to worry, you won't be alone! You will work hand-by-hand with our editors and we will send you guidelines and a template to make your life easier. Perhaps you would like to know that the best review will get a special prize by June 2024.

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