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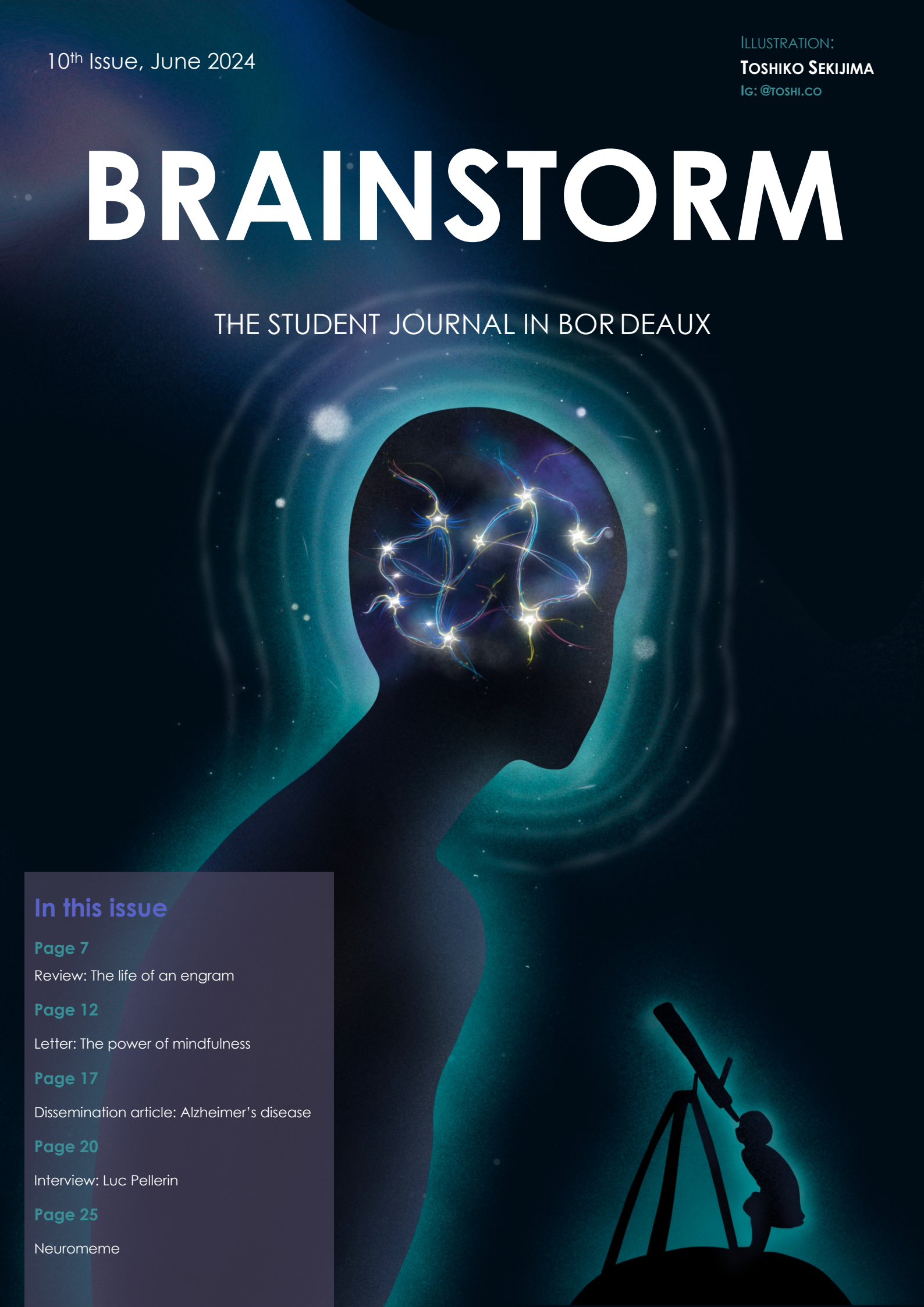

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VALUES

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All authors take responsibility for the content of their publication.

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The life of an engram

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Abstract

The study of memory has been greatly focused on finding the neuronal population responsible for the storage of memory. Researchers have mainly looked at how this population is chosen at the time of experience and how it evolves through time. The role of non-neuronal cell types, such as astrocytes, has also started to be considered key in the consolidation of memories. Understanding how normal memories are formed allows to understand how pathological memories, such as in the case of PTSD, can be created and ultimately may help to develop therapies to reverse this maladaptive state.

Keywords

Astrocytes, consolidation, engram, memory, PTSD

Abbreviations

ACC- anterior cingulate cortex

BLA-basolateral amygdala

CA1- cornu Ammonis

1, IEG- immediate early gene

PTSD- post-traumatic stress disorder

RObust Autonomous Modulation (ROAM)

Introduction

Reminiscing on the lost moments of childhood that come back when you get a whiff of your grandma's homemade cake? Or listening to that Paramore song that brings back all the heartbreak your 12-year-old-self thought you would never recover from? The experiences each of us go through shape us to the people we end up being later in life. And the fact that memory remains, and we can recall on such experiences, allows us to learn from them and adapt our behaviour.

Throughout the last 30 years, great breakthroughs have been made in the memory field. Initial studies with the simpler Aplysia, a mollusc containing only 20 thousand giant nerve cells comparing to the trillions mammalian brain has, demonstrated that even these giant marine snails are capable of retaining a memory (1). Later, numerous rodent studies followed, some of which I will introduce in this review, highlighting the great interest given to describing this fundamental part of animal behaviour, looking into how a memory is formed, stored, and retrieved.

Since the early 1900, the existence of a neuronal substrate for memory has been acknowledged and described as "...the enduring though primarily latent modifications in the irritable substance produced by a stimulus...", in the words of evolutionary zoologist Richard Semon (2). Although incapable of pinpointing these modifications at the time, his ideas remained for centuries when, with technological progress, it became possible to verify his theory. Thus, arised the engram, the population of neurons activated by an experience, that undergoes chemical and physical changes, and that are subsequently reactivated when cues referring to the experience are presented leading to memory retrieval. This engram has since been studied at different scales from the circuit to the molecular level and at different times as memory is dynamic and undergoes consolidation processes.

In this review I will address some of the most impactful discoveries in the memory field, focusing on how the engram changes over time, the role of the astrocytes in memory and how memory can become maladaptive.

Methods

Articles cited in this review were mainly found through Pubmed. Keywords included engram, engram AND astrocytes, PTSD AND contextualization. Reviews by prominent researchers in the field of engram narrowed down my research to the most important papers in the field. Most articles date from 2007 onwards.

Results

Scales of memory

To be able to study the engram, several strategies have been developed to tag this neuronal population. These strategies mainly rely on the use of immediate early genes (IEGs), such as cFos, indirect markers of neuronal activity, that drive the expression of a fluorescent marker in cells activated by a behaviour. By using this strategy together with IEG immunolabelling, Reijmers et al. showed that neurons in the basolateral amygdala activated during a fear conditioning paradigm were reactivated during memory recall, pointing to the existence of an engram (3). The causal link between the existence of the engram and the memory was later established by loss- and gain-of function studies. Liu et al. have shown for example that artificially activating dentate gyrus engram cells involved in fear conditioning leads to memory retrieval in the absence of cues for retrieval and conversely, silencing hippocampal CA1 engram neurons led to memory impairments when mice were exposed to cues related to the conditioning, as shown by Tanaka et al. (4,5).

Interestingly, loss- and gain-of-function studies often presented seemingly contradictory results depending on the brain region targeted and the time course of memory manipulation (6). This can be justified if one considers that the memory is dynamic in time and that it undergoes a process known as systems consolidation (contrasting with synaptic consolidation, a process that involves rapid changes after neuronal activation, altering synaptic strength and protein synthesis). In the process of systems consolidation, long- lasting changes in circuitry allow a memory to be safely stored and later retrieved. Brain-wide studies have identified how the functional connectome changes as memory consolidates, favouring more densely connected cortical areas and cortical-hippocampal-thalamic areas, and how these highly interconnected brain regions hold most power over memory expression, as inhibiting them leads to more marked memory impairments and reactivating key regions simultaneously leads to more accurate memory retrieval (7–9). In fact, neurons tagged during late retrieval, compared to those tagged during learning or early retrieval, were more likely to be reactivated at remote recall, showing that the engram is dynamic through time, from the moment the memory is formed to remote times (10).

This temporal shift can also be recognized in humans, as happened with the most well-known memory case, H.M (Henry Molaison), an epileptic patient that became amnesiac after undergoing a surgery to remove the focal point of his seizures, targeting part of the hippocampal area. Indeed, his amnesia was not for early life memories and not for all present time memories, as some experiences could still be learned and retrieved such as the organisation of the house to which he moved to after the surgery, highlighting the complexity of memory storage processes (11).

Of note, a significant number of studies in the memory field have peered into the engram on a circuit level, and fewer on molecular or synaptic scale. Some interesting studies on this have delved into the electrophysiological properties of engrams, showing higher excitability during retrieval (12), identifying CREB as a determinant of neuronal recruitment to the engram (13), and revealing increased connectivity between engram neurons with more and bigger spines (14).

Astrocytes' role in memory

The often-overlooked astrocytes have also been implicated in memory processes. This predominant glial cell type plays a pivotal role in the tripartite synapse, coupling pre- and postsynaptic neurons to modulate synaptic trasmission and plasticity. With the ability to manipulate astrocytes with optogenetic and chemogenetics, as well as the visualisation of their activity with calcium sensors, the role of astrocytes has become increasingly recognised.

Studies have found that inhibiting CA1 astrocytes during learning specifically impairs remote, but not recent memory recall and decreases activity in the anterior cingulate cortex (ACC) during retrieval, preventing remote ACC recruitment. Direct inhibition of CA1-to-ACC-projecting neurons also spared recent and impaired remote memory (15). Conversely, activating the Gq pathway in CA1 astrocytes enhances recent memory performance with increased neuronal activity in learning, accompanied by earlier recruitment of CA1-to-ACC projecting cells to the engram (16). These findings suggest that astrocyte activation in the hippocampus during learning is required for long-term memory storage.

Additionally, astrocytes change their transcriptional profile after fear conditioning in the basolateral amygdala (BLA) (17) and both neurons and astrocytes were shown to have calcium activity time-locked to freezing periods during fear conditioning (18), observations that further link astrocyte function and memory formation.

The existence of an astrocyte engram remains under debate, but recent work suggests that the astrocytes differentiate between engram and non-engram neurons, creating more connections with the former (19).

Maladaptive memory

What happens when memory processes fail? Psychiatric disorders such as post-traumatic stress disorder (PTSD) can arise after traumatic events and can be characterised by exacerbated fear responses in safe situations (hypermnesia of the trauma), while having difficulties retrieving other aspects of the trauma memory, such as the context (20). To mimic both these features, Kaouane et al. developed a model consisting of infusing corticosterone, the main stress hormone of rodents, in the hippocampus after fear conditioning. This resulted in an induction of PTSD-like memory impairments and an altered pattern of neural activation in the hippocampal-amygdala circuit, mimicking what has been reported in human PTSD studies (21,22).

The hippocampal dysfunction in this maladaptive memory was further shown as dorsal CA1 inhibition during a stressful event is sufficient to induce hypermnesia, as in PTSD-like memory, whereas promoting memorization of the context through dorsal CA1 activation in traumatic conditions enables the formation of normal memory, and thus prevents the development of PTSD-like memory (23).

Interestingly, the engram population has not been largely studied in the case of pathological memory. Knowing how the engram can store these memories resistant to extinction can, on one hand, shed light on the fundamental process of memory consolidation, but also give rise to therapies to prevent such persistent maladaptive memory.

Conclusions

Memory research experienced a great boost in the past years. Researchers have defined the neuronal population responsible for memory storage, have acknowledged the dynamic nature of the memory trace and have started to look at other cells, such as astrocytes, as contributors to memory maintenance. These discoveries have been useful in further characterizing processes of maladaptive memory as is the case with PTSD.

A lot can still be explored using increasingly detailed techniques, with higher temporal precision for the tagging of the engram and with higher spatial precision with microscopy tools allowing to view the engram at the synaptic level. This will allow to peer further into the molecular mechanisms that allow a neuron to hold a memory. Additionally, recent studies have also been exploring the importance of different cell types for memory maintenance, suggesting for example, a prominent role of inhibitory circuits in this process.

Understanding how memories are formed and maintained, and how they are extinguished, opens doors to therapeutics when considering maladaptive memories such as in PTSD.

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Freedom from the chain of repetitive negative thoughts: the power of mindfulness

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In everyday life, it is common to experience the feeling that our mind is running away from the present moment. This may be due to our focus on past events or our anticipation of future occurrences. This way of thinking can be so overwhelming that we are not always aware of what we are doing while our mind is engaged with our thoughts. These thoughts can sometimes take on a negative connotation, which can have a strong impact on our mood and generate feelings of anxiety and sadness.

Maladaptive thinking about the past and future, characterized by intrusiveness and difficulty in controlling thoughts, is defined as repetitive negative thinking (RNT; 1) and can be classified as a dysfunctional emotion regulation strategy (2, 3). For example, we can think about a failed date and wonder about what the other person was thinking of us. This type of thinking is called "rumination", because it is directed to the past (4). Conversely, one might consider the possibility of losing his/her job. In this case, the chain of thoughts is directed to the future and is referred to as "worry" (4).

Although these ways of thinking share many similarities, it is important to note that worry and rumination may not be identical. This is because engagement in rumination elicits sadness, whereas worry elicits anxiety. Furthermore, rumination has traditionally been examined as a risk factor for and associated feature of Major Depressive Disorder, or more generally of depressive disorders, characterized by loss of pleasure or interest in activities and a persistent feeling of sadness. On the other hand, worry is a defining symptom of anxiety and its disorders, especially Generalized Anxiety Disorder (5, 6), which is characterized by a constant feeling of fear, dread, and uneasiness. Together, worry and rumination represent an important risk factor for the development of psychopathologies (7). Moreover, repetitive negative thinking tends to exacerbate pre-existing symptomatology, with an enhancement in anxiety caused by excessive worry and an increase in depression caused by excessive

rumination. Finally, repetitive negative thinking is a common symptom of various psychopathologies (8), not only related to anxiety and depression.

The relationship between worry and rumination and psychopathology is not straightforward. Indeed, individuals without an official diagnosis may also use these maladaptive cognitive processes to regulate their emotions (9).

The question arises as to how an individual might ascertain whether repetitive thinking has assumed a pathological form that necessitates the seeking of professional assistance. One parameter that can be used to evaluate the functional impact of repetitive thinking is its frequency (10). It has been found that a dysfunctional way of thinking (i.e. worry) is much more frequent in a clinical population with a diagnosis of anxiety disorder than in a non-clinical population (11). Are you curious to check whether your concerns are clinically significant? A straightforward questionnaire, the Penn State Worry Questionnaire (12), can provide an indication of the frequency with which this mode of thinking occurs. You can find it on www.psychology-tools.com!

From a neurobiological perspective, what occurs in the brain when this maladaptive way of thinking is engaged? Neuroimaging studies indicate that repetitive negative thinking is associated with distributed brain regions operating within large-scale networks, rather than with a single structure (13). The brain areas most involved belong to the Default Mode Network (DMN; 14, 15), which is primarily composed of the medial prefrontal cortex, posterior cingulate cortex/precuneus and angular gyrus. The DMN is most active when a person is not focused on the outside world and the brain is at wakeful rest. It is therefore unsurprising that the period during which individuals tend to worry or ruminate more is before sleeping and in the first hours of the morning, as there are fewer distractive stimuli (16).

The causes of repetitive thinking have been the subject of recent research. Studies have indicated that difficulties in controlling attention can result in severe forms of negative repetitive thinking (17). In other words, when a thought crosses one's mind quickly, it latches onto it without being able to easily move on. This triggers a chain of circular thoughts that impact on an individual's well-being and efficiency, causing difficulties at work and in social relationships.

The main aim of this letter is to clarify that although repetitive negative thinking is a universal phenomenon, there are effective strategies for mitigating its impact. One obvious way to deal with this way of thinking is to start psychotherapy. However, it can be expensive (remember, your mental health is more important than money!) and hard if you are not ready to face yourself. So, what can you do if you are having difficulty in controlling your thoughts?

In recent times, there has been a great deal of discussion about mindfulness, a practice rooted in ancient Buddhist traditions and popularized in contemporary psychology. Mindfulness is the ability to pay attention to the present moment in a conscious and non-judgmental manner (18). Mindfulness can be learned through specific and rigid training, but it is also a natural predisposition (19). Recent studies have shown that mindfulness is an effective treatment for a wide range of psychological disorders and tends to significantly reduce the impact of repetitive negative thinking (20, 21). Indeed, several datasets suggest that mindfulness produces positive effect on well-being by counteracting the influence of dysfunctional emotion regulation strategy, such as worry and rumination (22, 23, 24).

Mindfulness is based on meditation (25), which involves focusing on the breath and the body movements that accompany it. In a typical meditation exercise, the focus is on the abdominal movement during respiration and the awareness of the breath. If you allow yourself to become distracted from the breath in a non-judgmental manner, you can then return to focus on your breath.

Why mindfulness is so effective in reducing repetitive negative thinking? It is important to note that although our mind may engage in repetitive thoughts about past experiences (rumination) or future possibilities (worry), the body stays in the present moment, where the events being contemplated are not actually occurring. The goal, therefore, is to establish a unified connection between mind and body in the present moment.

Several studies have demonstrated the beneficial effects of mindfulness on RNT across various populations. For instance, a meta-analysis (26) found that mindfulness-based interventions significantly decreased RNT and related symptoms of anxiety and depression. Similarly, a longitudinal study revealed that mindfulness training led to reductions in RNT and improvements in psychological functioning among individuals with a history of depression (27). Furthermore, neuroscientific research has elucidated the neural mechanisms underlying the impact of mindfulness on RNT. Functional magnetic resonance imaging (fMRI) studies have demonstrated that mindfulness practices modulate activity in the default mode network and in the prefrontal cortex (28, 29).

Unfortunately, the process of learning how to be mindful in everyday life is not so simple. It requires a lot of daily practice! In fact, when we are overwhelmed, for example with work, we may be inclined to put mindfulness practice on hold, and this could have a negative effect. It also appears that the difficulty associated with mindfulness is influenced by individual's personality traits (24) and can increase stress responses and negative emotions (30). Moreover, we need not believe that mindfulness is the solution to all our problems: some people may use mindfulness as a way of avoiding difficult thinking and critical life issues. It is important to remember that this approach cannot fix our lives completely.

However, it may be beneficial to attempt to use this approach to mitigate the impact of repetitive negative thinking on mood. As a psychologist, I always suggest this helpful approach to my patients (and to my friends, too). One option is to check out some podcasts online, like those from www.headspace.com (which you can also find on Netflix). This is a great way to try out mindfulness and see if it’s something you’d like to explore further. Another option is to try yoga with a qualified instructor. Yoga is one of the most popular mindfulness practices, and it can help you manage not only your mind but also your body.

Once the necessary practical skills have been acquired, it becomes possible to exercise mindfulness in each moment of the day, including while walking, working, and even during a particularly stressing situation.

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Alzheimer's Disease and Gamma Frequency

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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.

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What is Alzheimer's Disease?

Alzheimer's disease (AD), the most common type of neurodegenerative disease, largely affects older adults and primarily involves the deterioration of memory and cognition, as well as alterations in mood and personality. AD is a progressive disease that can begin decades before the first symptoms appear and is believed to be caused by a combination of factors such as aging, genetics, environment, and lifestyle. The initial symptoms involve mild cognitive and memory impairments, such as forgetfulness in everyday tasks. As the disease progresses, memory loss and cognitive impairment continue to worsen.

Causes and Physical Changes in the Brain

Our brains contain billions of neurons that send chemical and electrical signals throughout the brain and body. AD involves the death and disruption of these neurons, affecting the connections and communication between them, thereby inhibiting overall brain function. This primarily involves damage to the hippocampus and entorhinal cortex, two key regions involved in memory function. Other areas, such as the cerebral cortex, are also affected, impacting the processing of social behavior, emotion, and language.

It is believed that such damage and death of neurons is caused by the onset of multiple factors, one of them being the build-up of two molecules within the brain known as amyloid plaques and tau tangles, affecting both the outside (extracellular) and inside (intracellular) of neurons, and eventually altering physiology and function:

Amyloid Plaques: Result from the overproduction and inadequate clearance of amyloid-beta peptides (Aβ). Normally, this peptide is involved in neuronal growth and repair. However, when abnormal buildup occurs, they can misfold and clump together in spaces between nerve cells, creating plaques that can block synaptic signaling and lead to neuron dysfunction (1).

Tau Tangles: Involve the buildup of tau proteins within affected neurons. Under normal conditions, tau proteins support neuronal signaling through the stabilization of microtubules. In AD patients, tau proteins can become hyperphosphorylated (altered configuration), causing them to detach from their functional location within the neuron's microtubules and bind to other tau proteins. This results in tangle aggregates to form inside the neuron, hindering synaptic signaling, and leading to dysfunction in neuron-to-neuron communication which can create rippling effects on overall brain health and function (1).

Overall, amyloid plaques and tau tangles can alter neuronal signaling and communication which are fundamental aspects to efficient neuronal connection and health brain function. Ultimately, this can lead to neuron death and brain shrinkage, causing a wide range of cognitive and functional impairments.

Alzheimer's and Oscillations

Much like the synchronous rhythm of an orchestra, the brain exerts rhythmic patterns of electrical activity generated by synchronized neural firing. This heightened activity allows for efficient communication between different brain regions. In AD, synchronicity of neuronal activity is impaired, as evidenced by fluctuations in brain oscillations that differ from normal states. Alzheimer's patients exhibit increased slow oscillations (delta (0.5-4Hz) and theta (4-8Hz)) and reduced fast oscillations (alpha (8-13 Hz), beta (13-30 Hz), gamma (30-150 Hz)) (3). Gamma oscillations are directly linked to memory functions and cognitive tasks, particularly in the hippocampus (3). As memory loss is a major factor in the progression of AD, the reduction in fast oscillations may be a causal link (3).

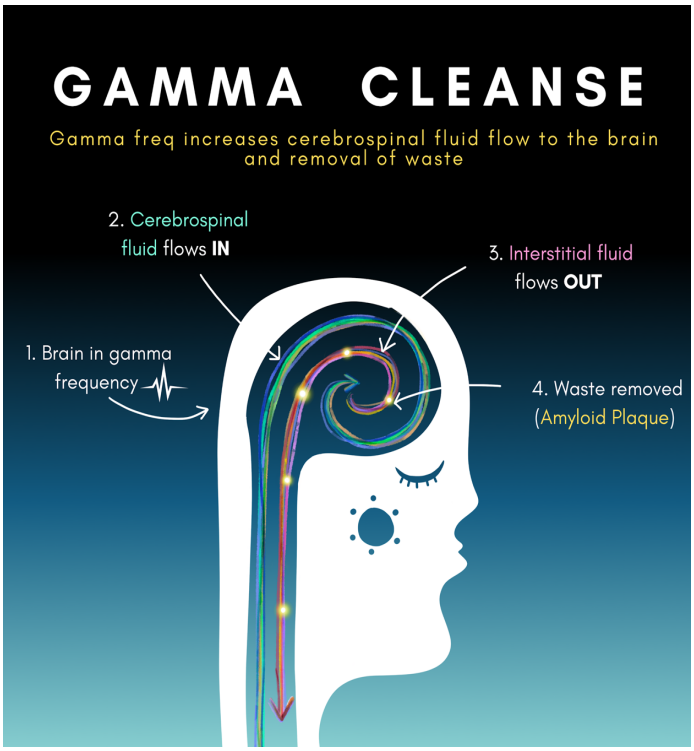

Figure 1: Potential mechanism of gamma frequency on the brain's amyloid plaque removal. Gamma frequency increases cerebrospinal fluid flow to the brain and removal of waste

Frequency Therapy

Research in both humans and mice has shown a potential new therapy to diminish the progression and development of AD through the use of gamma frequency treatment. Light flicks and sound clicks at the frequency of 40 Hz have been shown to reduce pathological states such as the presence of tau tangles and amyloid plaque build-up (3). Recent research uncovered this year at MIT has possibly revealed the mechanism behind why gamma frequency can be beneficial to the brain (4). Results show that gamma frequency increased activity of the glymphatic system, resulting in increased blood and cerebrospinal fluid flow to the brain, and increased interstitial fluid flow out of the brain (4). This induced greater "brain cleansing" through the removal of wastes such as amyloid-beta peptides from the brain. In Murdock's study, when mice were exposed to light flickers and sound clicks at gamma frequency (40 Hz), an increase in interneuron activity and blood flow to the brain was identified (4). This resulted in an increased inflow of cerebrospinal fluid and outflow of interstitial fluid within the brain, clearing away waste products such as the build-up of amyloid-beta peptides.

Conclusion

AD is a life altering disease known to alter one's consciousness and is an on-going issue that requires improvement in treatment. Research has now started to unravel the exciting potential that frequency therapy may play in the treatment and prevention of AD. Recent evidence revealed by Murdock's study has focused on the potential influence of glymphatic clearance of amyloid beta peptides through the use of gamma frequency stimulation. As research continues to look deeper into this topic we discover more about the pivotal role that brain rhythms may play in brain function. A big thank you to the scientists who have dedicated their time to uncover and treat this disease.

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What does the brain eat?

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Our brain represents only 2% of our weight. Paradoxically, it consumes 20% of our available energy. So it is relatively small but a very energetically expensive organ. The brain is a bit clumsy at storing energy, so the energy it uses is found circulating in the blood vessels (the glucose we obtain through food), so it needs constant irrigation. Most of this energy is consumed by neurons. This is surprising for a very simple reason: neurons do not have privileged access to blood glucose, since there is a barrier of astrocytes separating them. In other words, neurons are hungry for glucose but to obtain it they need to communicate with astrocytes to be able to work properly. This is basically what the lactate shuttle theory proposes. Who better to understand it than Luc Pellerin, one of its fathers?

Luc studied in Canada. He received his PhD in biochemistry from McGill University, specializing in neurochemistry. He did a postdoc at the University of Lausanne (Switzerland), in the department of physiology, joining Pierre Magistretti's laboratory, where he was gradually promoted. He then became assistant professor, finally associate professor and head of the Department of Physiology. Two years ago, he accepted a position as professor of biochemistry and molecular biology at the University of Poitiers. And he will soon become director of unit U1313 at INSERM, where he will explore metabolic interactions in transplantation.

Juan García Ruiz: The brain consumes a large part of our available energy. How does it manage to obtain it?

Luc Pellerin: The classic version since the 1950s results from the work of Henry McIlwain, who showed that apart from glucose there were very few energy substrates that could fuel brain activity. Since then, several exceptions have emerged. Lactate has been shown to serve as a complementary energy substrate to glucose in certain situations. For example, immediately after birth, during intense exercise, during prolonged fasting or in pathological situations such as diabetes. Glucose itself remains the main substrate, but the idea that is beginning to emerge is that it is not always used directly as an energy source, but that there are metabolic exchanges between brain cells. This new hypothesis has been called the lactate shuttle and describes how some cell types, such as astrocytes, convert glucose into lactate, which is in turn transferred to other cell types such as neurons, capable of using it as a complementary energy substrate.

JGR: What is the ratio of glucose to lactate used by neurons as an energy source?

LP: The answer is still unclear. Early estimates suggested that neurons consume mainly glucose and relatively little lactate. Later in vitro experiments suggested that when a neuron is presented with lactate and glucose at the same time, about 75% of ATP production during oxidative phosphorylation comes from lactate and 25% from glucose. But this is under basal and in vitro conditions. During activation there is an increase in glucose consumption in astrocytes, much less in neurons. This points to the fact that when energy needs are higher, neurons are likely to use lactate preferentially. When we look at the distribution of energy consumption by the different cell types, neurons consume about half of the available glucose, which does not correspond to their high energy needs. This suggests that what is needed to fill the missing energy portion must come from another substrate such as lactate. One question that arises is related to the fate glucose: is it devoted entirely to support energetic activity or it can have other functions? And here again there is evidence suggesting that some of the

glucose consumed is not metabolized in oxidative phosphorylation but goes through the pentose pathway to regenerate NADPH. So there are other functions for which glucose is essential.

JGR: How would you explain from an adaptive point of view that neurons need to go through astrocytes to access energy? Wouldn't it be much simpler for them to access it directly?

LP: This question arose relatively early on when the lactate shuttle hypothesis was proposed. The idea that neurons accessed glucose from the extracellular space was straightforward, so we used to think this was the case. Why bother having an intermediate like the astrocyte if the neuron can extract glucose directly? But if we consider that glucose can be used for other things and energy is obtained by other means, this implies that we are not dependent on a single substrate for everything. In this case, lactate could be used to produce energy, while glucose could be used to regenerate NADPH or synthesize neurotransmitters. The advantage is that the functions are decoupled and not solely dependent on one molecule. There are also advantages from a metabolic point of view. Lactate is converted to pyruvate and then goes directly to the Krebs cycle to produce ATP. In this case the neuron does not have to make any metabolic investment before going to the Krebs cycle to produce energy. In fact, the first step of glycolysis is glucose phosphorylation into glucose-6-phosphate via a hexokinase that requires ATP. So to recover energy from glucose, the neuron has to first invest some energy, which is a problem if it is already in a state of energy need.

The second problem is that glucose has to go through glycolysis before entering the Krebs cycle, and glycolysis is not a very rich ATP source. In other words, before reaching the step where we can produce a lot of energy (the Krebs cycle) there are a large number of steps (therefore a large investment of time) that makes it less efficient. Hence the advantage of having a faster energy source that does not require an initial energy investment. In addition, the astrocyte appears to be more oriented towards lactate production, whereas neuron gene expression is rather oxidative (energy consumption). Protein expression suggests that the coupling between the two processes is advantageous. Delegating glucose metabolism to the astrocyte seems to benefit the neuron, allowing it play other roles.

JGR: To what extent does the scientific community accept the lactate shuttle theory?

LP: When we proposed this hypothesis 25 years ago, we did not have a very warm welcome because we went against dogma. There were violent controversies, as happens with any emerging hypothesis. You need to bring new arguments and produce new data. Over time more and more scientists began to accept it. But there always remained a small nucleus of people who did not accept the hypothesis and tried to provide arguments to discredit it. I consider this to be a minority. I think that for most people in the field of metabolism or in the field of neuroimaging, this hypothesis is able to explain a great number of phenomena. But this questioning is actually a positive thing, because it pushes us to go further and to look for new evidence that allows us to better understand the phenomenon. The question is always the same: it is not a matter of finding out whether the lactate shuttle exists or not, but of understanding what really happens and how the brain uses its energy. At the moment it seems to be going in the direction of the lactate shuttle, but this theory could change.

JGR: What is your current research topic?

LP: We will soon publish an article in the journal PNS in which we provide evidence that inactivation of the transporters that enable lactate transport from the astrocyte to the neuron interfere with brain metabolic responses and with behavior (with learning and memory). So this phenomenon seems essential for specific brain functions. At first it was thought that glucose played a key role, now the focus shifts to lactate. The next step is to understand what is the role of glucose by using the same approach we used for lactate: what happens if we inactivate glucose transporters, for example, in neurons? Would we have the same effect as for lactate transporters? Probably both substrates (lactate and glucose) are essential but play different roles.

JGR: What are the frontiers of this field?

LP: There is something that remains unclear. We know that lactate is a good neuronal energy substrate. It is taken up by neurons through a transporter called monocarboxylate transporter type 2 (MCT-2), which is expressed on the surface of the plasma membrane. It has been shown that MCT-2 is also found in synapses, specifically in the postsynaptic component. This is curious: since it is the transporter of an energy substrate, why is it there? Is there a specific energy requirement at the synapse?

Secondly, it has been shown that this transporter can associate with AMPA glutamatergic receptors (GluA2 subunits) in the postsynaptic membrane. This raises another question: in addition to being an energy transporter, can it regulate synaptic transmission? Are these two functions linked? There are other unresolved questions. For example, what regulates the expression of lactate transporters in astrocytes? This has already been studied in neurons, where it is translationally regulated by trophic factors such as BDNF (editor's note: brain-derived neurotrophic factor). But in the astrocyte it has not been investigated. Is the expression related to synaptic plasticity? What are the signals involved? As you can see, there are still many unknowns. And the ideal would be to be able to translate all this to humans, to look for possible therapeutic approaches.

JGR: What have you learned from your years of experience in science?

LP: Scientific training gives a Newtonian vision of things: there are rules and laws, and by applying them, we can make discoveries. With experience I realized that, although this is very useful, in the end the world is not so predictable and that there is a part of imponderable, of imagination, something that appeals more to intuition and creative sense. I have learned to develop these aspects and not to limit myself to the purely rational, but to leave room for imagination, for freedom of thought. Sometimes solutions to problems do not emerge from a purely rational approach because there are many parameters that we do not control.

I have also realized that there are multiple ways of looking at the world and that all of them can contribute to our understanding. I will share with you a little anecdote. When I started my postdoc, I worked with a Chinese doctoral student. It was very difficult for me to understand his reasoning, but in the end we always came to the same conclusion. His approach was completely different, but we always arrived at the same result. You have to take all this into account. Sometimes, only with different points of view can we find the solution to a problem that is not possible to solve with our own way of seeing things. I try to foster this vision in my team, which has people from very different backgrounds to avoid the in-breeding that makes everyone think the same way.

JGR: How do you see research in Europe compared with USA and Canada?

LP: In Canada, the size of research is still relatively small compared to USA. So we always keep our eyes on what is happening in the United States. But I did my thesis in Montreal, in an English-speaking university, and it was like a continuity of what was going on in the United States. So when I talk about North American research, I don't really differentiate between Canadian and American culture. But there is a big difference between North American and European one, which actually led me to do my postdoc in Europe. In North America, research is very results-directed. The notion of efficiency is always present. This introduces extremely high pressure, because not only do you have to find the funds for research, but you also have to produce. Although it has its advantages, one should not forget its disadvantages. One of them is that the time for reflection becomes too short. We come up with short-term strategies to avoid starting projects that do not produce results quickly. When I came to Europe 25 years ago, I saw something different. I had longer periods of reflection, and although productivity was lower, I could aspire to have a greater scope. This vision of Europe is slowly disappearing. But that vision is perhaps what allowed me to propose the lactate shuttle hypothesis. All the work necessary to develop the hypothesis and reproduce the experiments, and which allowed us to publish in major journals, spanned decades. This would not have been possible in any other context. The North American phenomenon of efficiency, productivity and profitability is reaching Europe, which means that long-term research is disappearing.

We have less and less time, and we cannot afford a project that takes 4 to 8 years to produce its first results. We have to adapt to this new way of working, but I deplore it a bit. The ideal would be to keep the best of both worlds. What I did not like about Europe was that there was a lot of waste and little efficiency. Now we gain in efficiency but lose in long-term thinking.

JGR: What would you tell to young researchers to encourage them to do research?

LP: You may not like my answer. In research many young people are solicited, but in the end very few are chosen. If you are not clear about that, maybe it is better to forget about it. If you start to doubt yourself, think it's not for you or you're not ready to make the effort, maybe it's not for you. It has to be a passion. You have to be convinced that this is what motivates you, what makes you get up in the morning, what makes you want to go back to the lab even if sometimes you get discouraged. When you are really convinced that this is what you want to do, go for it. But the conditions are so difficult and the rewards so few that there is no point in pursuing this kind of career if you are not completely sure. You have to be aware of the reality of things and I don't want to take anyone for a ride. When you are sure, what you need is to find mentors, people who will support you and who can help you in the most difficult stages. Research is an interconnected field, a system in which you need to build your own network.

JGR: Would you recommend a scientific book that left a mark on you?

LP: I am going to recommend a book entitled Discovering, written by Robert Scott Root-Bernstein. It was given to me as a gift by a friend who was doing her thesis when I was defending mine, just before doing my postdoc. It's a reflection on what makes some scientists make discoveries and others don't. What is the role of education, the way one is trained or the approach to science, in success? There was a chapter on affiliation. If you look at Nobel Prize winners, there are often connections. People who come from the same laboratory pass on their knowledge to others, and then to others, and so on. The idea is that there is a certain way of conceiving scientific research. And since this vision is passed on from generation to generation in the same laboratory, this predisposes them to have a higher probability of making an important discovery. He also explains that among the Nobel laureates, many people had other passions besides science. For example, there are many musicians.

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

LP: The important thing, in my opinion, is to enjoy science all the time. It is a difficult career. Don't expect recognition from your environment, from your academic environment, from your hierarchy. Your reward should come from the pleasure you get from doing what you do. This has been my leitmotiv from the beginning. I had been hoping for a long time that at some point there would be recognition from my colleagues, but I realized that it doesn't work that way. It would be a shame to sacrifice your whole career trying to get this prestige, knowing that it may never happen, and that you've really sacrificed and put in a lot of time and not really enjoyed it. The idea is that you have to have fun doing research, really do what interests you, and not do it because others ask you to or because you want to please those who fund you. Pursue your interests, pursue what motivates you.

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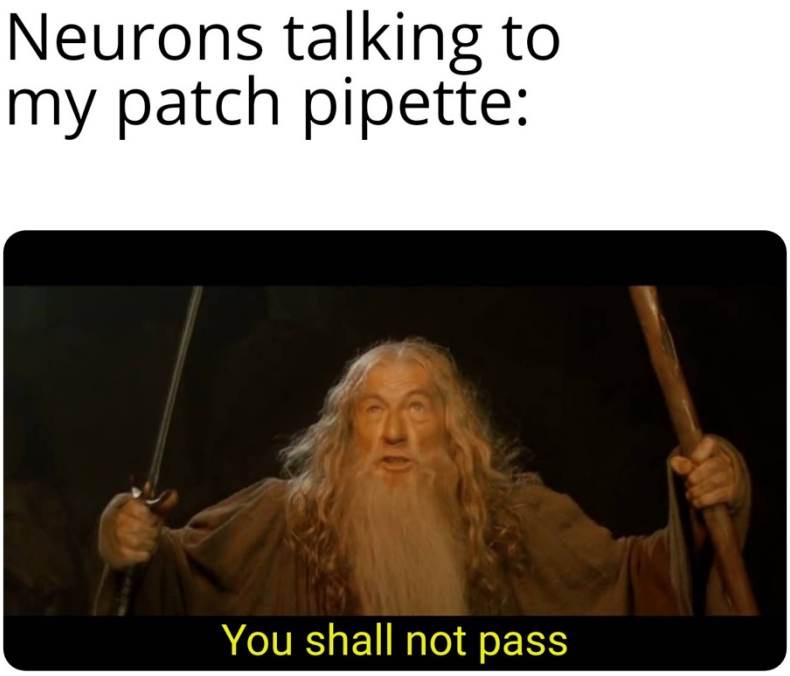

Simon Lecomte, 3rd year PhD student at the IINS

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

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

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