Time factor in neural learning processes

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Abstract. This paper explores the role of neural plasticity and environmental influences in cognitive development and learning processes. The brain's ability to reorganize its synaptic connections is examined both during embryonic development and throughout the lifespan. The first part focuses on the impact of the environment on neural plasticity, from cellular influences to epigenetic ones. The analysis also includes the effects of epigenetics on cognition and the implications of environmental stress on brain function, with particular attention to the dendritic spines changes. The second part investigates how the environment continues to affect neuronal changes through learning, emphasizing the importance of timing and the synchronization of external stimuli and synaptic modifications. This study suggests that understanding the timing and coherence of synaptic activations is crucial for optimizing learning and improving cognitive rehabilitation strategies. A timing approach to neural plasticity, which is influenced by temporal and environmental factors, could have also significant implications for education, mental health, and therapeutic practices.

Keywords. Neural plasticity, leaning processes, timing signals, synchronization

Introduction

Understanding the mechanisms by which the brain adapts to new experiences is one of the most challenging and fascinating areas of neuroscience. The ability of the brain to remodel itself, known as neural plasticity, is fundamental to the processes of learning and memory. This paper explores how neural plasticity functions across the lifespan, focusing on the key role that environmental factors play in shaping synaptic configurations and how these changes contribute to cognitive development and learning. Specifically, we will examine the concept of neural plasticity from a neurophysiological perspective, investigating its relationship with synaptic modifications and how these are influenced by timing and external stimuli.

In Section 1, we discuss the mechanisms of neural plasticity during brain development, exploring how neurons migrate, differentiate, and establish synaptic connections. This section highlights the critical role of the environment at different levels, from cellular interactions to epigenetic influences. Subsection 1.1 focuses on the early stages of brain development, particularly the role of glial cells and the importance of environmental stimuli in shaping neural architecture through processes like synaptic pruning. The discussion also delves into the impact of epigenetic factors, such as parental

behavior during pregnancy, and their long-term effects on brain development. In Subsection 1.2, we extend the analysis to neural plasticity throughout life, focusing on how experience and environmental changes continue to shape synaptic connections, particularly in learning and memory processes.

Section 2 focuses on the relevance of timing in neural plasticity. We analyze how the synchronization of neural activations, often referred to as synaptic timing, is essential for effective learning and memory consolidation. This section introduces the paradigm of spike-timing-dependent plasticity (STDP), exploring how precise timing between stimuli and neural responses enhances or weakens synaptic connections. Subsection 2.1 investigates how learning is related to timing of neural information processing and proposes that neural plasticity is not just a matter of structural changes but also of temporal coordination across neural networks. Subsection 2.2 examines the relationship between timing, conscious agency, and the perception of voluntary versus conditioned learning. The section concludes by proposing that the sense of agency in learning is modulated by the temporal architecture of external stimuli.

Throughout the paper, we aim to demonstrate how the intricate interplay between genetic, environmental, and temporal factors contributes to the brain's capacity for learning and adaptation. By understanding these mechanisms about functioning of the human brain we could also explore potential applications in education, cognitive rehabilitation, and mental health interventions.

1 Neural plasticity features and the role of the environment

The basic concept of new neuroscience is that over time the brain is always willing to reform and change. The brain, like life, is not a static system, but a process of self-creation known as *autopoiesis*. It was the great Polish neuroscientist Jerzy Konorski (1948) who used the term *plasticity* in 1948 to describe brain changes, which are due to the strength of connection between neurons expressed by the influence of experience. Previously, Ramòn y Cajal (1894) had argued that the ability of neurons to mature and their power to create new connections can explain learning. In the early 1950s, several studies had also shown that "repeated administrations of an electrical stimulus to a nerve pathway were able to alter the synaptic transmission in that way generating a neural plasticity, that could be associated to learning improvement and emotional subjective responses" (Le Doux 2003)[1].

I cite this sentence that exposes a strong claim of the author, because it contains the most relevant elements that we are going to deal with. The possible connections between neural processes, learning and conscious perception is one the most complicated themes debated in the philosophy of mind. I will expose, in the following many different researches and theories that explore the problems involved in this connection, and I will try to explore it through a new situated and timing-based paradigm.

The work of Larrabee and Bronk (1947) and the one by Lloyd (1949) were also relevant in shedding light on neural plasticity. Thompson and Spencer (1966) showed

[1] Le Doux offers a fertile account based on an accurate analysis of neurophysiological processes in order to explain the construction of the self and the main features that we can ascribe to subjectivity. But his assumptions are limited to a descriptive level, so that they cannot have the causal powers that they are supposed to have in his account.

evidence that synaptic modifications could explain learning. John Eccles studied changes in the synaptic activation to motivate an interactionist dualism neurobiological perspective, which he developed together with Karl Popper in *The Self and Its Brain* (Popper and Eccles 1994)[2].

1.1 Plasticity during brain development

During development, after a period of intense proliferation, nerve cells emit extensions, the axons, which navigate under the action of recognition molecules, heading to a certain region and coming into contact with other cells. Through the process of *migration* neurons develop and reach their final position in the different levels in the neural tissue assuming their morphology and function. Morphological neural differentiation occurs during the development of the axon migration process (stretching and reconnaissance) to target neural cells that have receptors (NMDA) on their synaptic membrane that "approve" such a link. This differentiation is conditioned by position of the cells within the brain's stratification and the presence of neighbouring cells (Le Doux, 2002).The brain configurations that originate in this way are only partly genetic, since we do not have enough genes to codify for all the synaptic junctions we possess (this argument already provides a solid basis for a counterargument of a rigid materialistic innatism).

There is an active role of glia cells in structuring channels for neural migration. This is a very important discovery because the protagonists of neural functions used to be associated only with neural structures. But now a more relevant role is attributed to the glial cells, and this demonstrates another relevant role of the environment, in this case of the neural cell and its surroundings. These kind of glial cells are important for the nutrition and support of all neural structures, but they are also truly relevant in structuring channels and pathways during the development of the brain that neural cells go through in the process of migration. Also, at a broader level we can consider the active role of environment: the context, the situation in which the subject is, impacts on the activity of glial cells and neurons through epigenetics processes (as we will see in next section), by modulating their gene expressions.

At this point electrical activity, partly intrinsic and partly driven by stimuli of the environment, becomes essential to strengthen some connections at the expense of others and thus build that fine architecture that allows our brains the most sophisticated performance. Functional and morphological adaptation driven by electrical activity is crucial in learning processes. This extreme ability to grow and shape the connections typical of development persists for the rest of life, albeit to a more limited extent. It consists of structural changes that underlie the processes of learning and memory, both motor and cognitive, and the processes of adaptation of the organism to changing environmental conditions: activity-dependent mechanisms that govern the formation and elimination of synapses.

One of the most important processes of change in the spacetime architecture is *pruning*. This process cuts the overabundant neural structure to sculpt the neural

[2] This interesting perspective is carried out through a dialogue between the two authors, who argue for the existence of three different worlds, each one irreducible to the others. Eccles then describes the existence of functional modules, some closed and some open. The latter ones are able to share contents with other modules. This claim is the base of global workspace theory.

architecture. Many major mental illnesses start to emerge in adolescence and may be caused by aberrant synaptic pruning. Although we are only beginning to unravel the ramifications of synaptic pruning in the human brain, this process clearly has significant consequences for normal human brain function and may provide key insights into the causes of some devastating and mysterious neuropsychiatric diseases.

Modifications of this process seem to be involved in some cognitive diseases that concern learning and social abilities, like autism and schizophrenia. Disordered synaptic pruning could, in fact, explain the age of onset of schizophrenia; a group of researchers (Rose S.A et al. 2016) published genetic and experimental evidence supporting this association. While schizophrenia seems to be characterized by over-effective pruning, autism disorders seem to be connected to a lack of effective pruning.

Coinciding with specific patterns of pre-synaptic and post-synaptic activity, functional changes in the efficiency of synaptic transmission, known as Long-Term Potentiation (LTP) or long-term depression (LTD), are induced. These phenomena are associated with changes in gene expression in the neurons involved, followed by structural remodeling of connections: the number of contacts between neural cells increases as a result of LTP, decreases as a result of LTD. Neural plasticity is believed to initiate initial changes in the efficiency of synaptic transmission, induced by precise patterns of nerve activity. These functional modifications are followed by structural remodeling processes that lead to the new training or elimination of connections. According to a theory put forward by Donald Hebb (1949)[3], synchronous activation of pre-post synaptic neurons induces a strengthening of connections, while the activity that is mismatched over time tends to reduce their efficiency.

Epigenetic factors

Environment and experience in neural networks are very relevant during development of the brain, particularly because configurations that originate during the process of migration are only partly genetic, because we do not have enough genes that encode for all the synaptic junctions we possess.

The environment can modify function, more precisely it can amplify the activity of a gene or reduce it through biochemical mechanisms: methylation reduces the activity of a gene, acetylation amplifies it. Phenotypic aspects could be derived from previous cells without changes in genetic sequences..

Epigenetics is the research field that focuses on these processes and lots of recent studies investigate the deep meaning of this. This in fact implies a revolutionary perspective that has a strong impact on the models and methodology of neural investigation. One of the main claims of epigenetics is that there is a sort of footprint, or more precisely an epigenetic mark, which changes the activity of either a gene or a group of them, and this comes from the past of the subject. The molecular response to a specific situation could be responsible for the degree and way of activation of a specific gene. This means that, through epigenetic mechanisms it is possible to modify the activity of genes, giving them the input to generate one or more of those fragments that I mentioned before, the epigenetic marks, the genes can therefore be regulated in this way.

[3] This work is very important, not only for the study of neural plasticity, but also because it opens the possibility of a treatment of timing windows of activations of neural units.

Even if the complexity of the molecular processes that let this happen, is the root of a strong debate on this kind of explanation, the epigenetic impact is evident in many situations. In my opinion it is also a very interesting topic for the purpose of the present analysis, because phenotypic aspects, under this perspective, are one side of the environment, as they derive in some way from it and reflect some aspects of it. Therefore, a comprehensive understanding of subjective faculties must include an adequate analysis of this deep connection.

An important factor of the environment that is crucial in the development of the brain is parents' behavior, as lots of epigenetic studies demonstrate (Weaver, 2004). In particular, the mother's behavior during pregnancy plays a relevant role in structuring the development of the children's brain. The first nine months of life are very relevant to determine the fate of our entire lives. The fetus receives everything that the mother transmits, positive and negative, from food to substances that she can take, to the degree of work stress, for example through levels of glucocorticoids. I speak of glucocorticoids because they have been marked better, but there are definitely other molecules that pass the placental barrier and reach the fetus going to genes.

The fetus develops many cells of great variability, complexity and behavior, and the psychophysical state of the mother, for instance a depression or some other pathology, can cause alterations in these delicate codes.

Thus, during the development of the brain, experience and environment are allied with genetics to originate effective synaptic junctions and to determine learning.

1.2 Neural plasticity during life

During life neural plasticity occurs thanks to the environment too. In the adult, neural plasticity is mainly related to synapses. Here, as a result of experience there is a strengthening or weakening of the effectiveness of the transmission of the nervous impulse from one cell to another. These changes can range in duration from milliseconds to months. From a structural point of view, synapses, especially those that form on dendritic spines, can increase or decrease their surface area or vary in number. In addition, there may be variations in the number of synaptic receptors, or the molecules released into the synaptic space, like neurotransmitters.

Dendritic spines are small neural membranous protrusions on a dendrite surface that typically receive input from a single axon. Dendritic spines contain neuro-transmitters and receptors. Signaling systems essential for synaptic function and plasticity have different sizes and shapes. In this scheme we see the mainly relevant shapes. They appear in those circuits that are more used, so they are useful markers for learning effects.

Within a neurophysiological analysis we talk about neural circuits and systems. A circuit is defined as a group of neurons that connect through synaptic connections (observed from the outside to investigate certain functions). Instead, a system is defined as a set of circuits that perform a given function. Neurophysiological investigations describe sequences of impulses and try to ascribe a functional meaning to them, indirectly connecting a class of activations to previous stimuli, occurred in a specific time window that allows for this causal explanation. Here, I wish to point out that these methodologies have a problematic epistemological aspect. In fact, when we talk about a function, in neurophysiological analysis, we refer to a relation between some neural activations.

This functional attribution is based on a perspective cut, which means to isolate activations (that we choose as relevant in the process that we are examining) and to consider some of them as origins or inputs and the others as responses or outputs.

In order to better understand this aspect of the enquiry in neural functions, we need to remember that the neural system is always active and works in synergy with many other systems. Therefore, the level of neural circuitry that undergoes certain functions depends on a functional and finalized delimitation of the observer. To explore a function and a target, the observer operates a cut, selecting a portion of the dynamical structure, the part that seems to be mostly involved in the process he is interested in. *Involved*, under this perspective, means that a group of neural cells is active in a time interval that can be considered causally determined by the stimulus that hit the network in the previous moment. This could be considered a coherent activation in a stream of activations that come after a specific stimulus (and in an experimental condition, stimulus structure is controlled, as the features of the output related to it). The intrinsic dynamicity of the neural system (*i.e.*, the constant activity that depends on the morphology of the neural network and the shape and type of function that each neural cell exhibits), as well as its extrinsic dynamicity (that depends on the correspondence between the structure and timing of stimuli), imposes an epistemological relativization.

The differentiated structure and morphology of neural cells, on the other hand, does not depend on a perspectival choice of the type just exposed. We can, in fact, observe and describe a lot of shapes of neural cells and their relative positions, and we can also observe the level and typology of neural tissue in which that group of cells is located. These descriptions of the features of neural cells, material connections, and neural tissue are based on static observations, and they don't depend on a perspective cut, like in the case of functional circuits, but they are objective descriptions of static components. So, we can see that the epistemological problem seems to be connected with the functional description of dynamical processes.

Thus, at this level of explanation, the diatribe concerns the weights that we can associate to the different functional units in the network that we are considering. This distribution implies a stance regarding the weight and the role of the different inputs from the environment that influence the individual network in a specific way. We could say that different neuro-computational approaches differ from each other with respect to how this distribution is construed. Computational explanations presuppose a distribution of weights on which the system computes, and these weights represent, in some way, the relevance of environment features for the individual system, in a specific context. This implies a stance about the boundaries of the subject and his identity. There are two basic neurophysiological theses in this regard, that I would like to briefly summarize here.

The first one is Neural Darwinism, the second one is strong neural Darwinism, which will be discussed later. In this model the self is not built from simple elements to form a complex. Rather, it is selected from a complex structure by the possibilities in the environment. This interesting theory of brain development during life was formulated by Gerald Edelman, in a book called *The Mindful Brain* (1978)[4]. It was then

[4] The theory exposed by Edelman here retraces the immunology functions of the body and applies a concept of selection and adaptation, taken from an evolutionary paradigm, to the

revised and extended in a subsequent famous work (1987) by the same author. The name Darwinism alludes to the fact that this theory is presented by the author as an extension of Darwin's natural selection theory. More specifically, it is an extension with respect to the process of neural development in the human system. The analogy is played on different levels and it starts from the previous studies of the author in the field of immunology (Edelman 1987).

Even if it is necessary that different levels of explanation contribute to research on brain workings, neither is there a spiritual claim, nor a reification of language contents. Edelman refuses the linguists' explanation for the genesis of mental faculties. He argues that the integration of functions and responses, to be valid and correct, must also respond, without the involvement of language, to evolutionary requirements, as demonstrated by advanced neurophysiology. There must be some signs of the evolutionary process in the development of the brain, and some of them can be investigated.

Before approaching his perspective in more detail, we need to anticipate one of its crucial notions: the neural map. I will briefly introduce this concept in order to better understand Neural Darwinism: a neural map consists of an organized topological structure, and the activity of groups of neurons and fibers in the brain of an organism. The neural map is the functional unit of a neural network that corresponds to a function that manifests perceptual or motor output. We can talk of two hierarchical levels of neural maps. The first level, the most basic one, is the local neural map and it corresponds to an interconnection of smaller spatial and numerical portions of neurons that perform more specific and limited functions. The global neural map, more plastic, corresponds to an interconnection of different local maps.

We could think of the global map as the road network of a city that interconnects the local neighborhood networks (local maps). The closure of a street in a neighborhood involves the redefinition of the whole traffic at the city level.

In a nutshell, the groups neuronal selection theory is based on three main evolutionary principles:

1. The first principle refers to the fact that there is a neural selection in fetal development; on this basis, a primary repertoire of functional maps is constructed during development of the fetus, thanks to genetic and epigenetic factors.
2. The second principle refers to neural selection that depends on the animal's experiences during its existence; this provides for the construction of a secondary repertoire of functional configurations of maps and circuits.
3. The third principle, the most debated one, refers to the existence of the *re-entry mechanism*. This means that the experience generates some individual perceptions in presence of some specific conditions of the external world. These perceptions correspond to the formation of specific signals about individual conditions that are sent back into the maps of neuronal networks and continuously contribute to update them, producing their continuous change at the level of synaptic connections.

If we consider all these principles together, we get a synthetic view of neural Darwinism theory. The entire process is based on selection and involves populations of

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neurophysiological functions. But this analogy especially in its extension to psychological function is nowadays very debated.

neurons engaged in topobiological competition. A variable population of groups of neurons in a specific area of the brain is defined as the primary repertoire, which includes networks of neurons that emerge through somatic selection processes. The genetic code does not provide a precise and detailed pattern for the formation of these repertoires, but rather imposes a set of constraints on the selection process.(Edelman 1988).
In order to explore more deeply the process of neural selection in the brain cells, we can refer to three fundamental assumptions of the theory: 1) Redundancy: there is in every individual an overabundance of synaptic endowments. 2) Reinforcement: there are reinforcement processes of the synapses most commonly used. 3) Subtraction or degeneration: there is a removal process of unused synapses.

From this point of view the baby has an overabundance of synaptic connections; in this "synaptic cloud" every experience and learning process contributes to cut ineffective or useless ones and to reinforce the useful ones. Then, experience in the environment sculpts the subject, by selecting, among the many synaptic possibilities, only some of them and reinforcing the most used.

There is also a more rigid version of the neural Darwinism model, called *Strong Neural New-Darwinism,* which maintains that neural activity contributes to avoid neural death, which is to result in the death of those cells that do not receive input. Neural activity, therefore, in this model, preserves from death existing patterns. The focus is on the role of neural death in the structuring complexity of synaptic ramification and its contribution to the demarcation between cortical areas, and not on the reinforcement and re-entrant processes.

Neural plasticity, the changing in synaptic connections through dendritic spines, on a molecular level of explanation, occurs by simultaneous input and by the presence of neurotrophies (NGF, BNDF, N3, N4) or function stimulants and growth factors. However, they act in an anterograde path, that means they contribute to the reinforcement of those junctions (which make up observable circuits) that have proven to have effective outputs. So, the process develops according to the following steps: at first a stimulus occurs, an evaluation of the effectiveness of a useful output is required, the reiteration of some output in concomitance with a situation generates the reinforcement and production of neurotrophy. The result of this process is precisely what in neurophysiology is called *learning.*

More briefly, neural plasticity develops by virtue of neurotrophies, growth factors, which act in an anterograde sense: they contribute to the reinforcement of those junctions that had proven to have effective outputs. This means that there must be an integrated evaluation that judges whether an output related to a particular stimulus is better than another one with respect to the best functionality of the whole system.

Features of environment and complementary systems

The evaluation of efficacy appears to be a crucial aspect to have a satisfactory output in a specific context. What it means to be effective and what it means to evaluate the relevant parameters of a situation in order to perform an action is very debated, and I will take up this problem in the following sections, not only from a neurophysiological point of view, but also from a psychological point of view.

The role of hormones is another important aspect, which heavily influences neural changings, since intrauterine life and during the whole subsequent life. These molecules work in synergy with some neurotransmitters to modulate the activity of

neurons. For example, the brain hemispheres of a healthy woman vary in volume during the menstrual cycle depending on hormone levels. It has been observed that hormones, both progesterone and estrogen, play an important role in regulating trophism: in women these neurons are going through cycles of hypertrophy.

There is another relevant system which is a complementary element to the work of the neural system. This is less studied, and it has a lot to do with pleasure and satisfaction. It is known as *endocannabinoid system* and it refers to the trade of endocannabinoids and molecules. Endogenous cannabinoids work in synergy with many other molecules, and especially with hormones. Endocannabinoids are lipid-based retrograde neurotransmitters that bind to cannabinoid receptors (CBRs) and cannabinoid receptor proteins that are expressed throughout the vertebrate brain and peripheral nervous system. The endocannabinoid system appears to be involved in regulating physiological and cognitive processes, including fertility, pregnancy, pre- and postnatal development, various immune system activities, appetite, pain sensation, mood, and memory. But here I just want to mention to highlight that there is a strong impact of the environment on the individual neural system, and this occurs by the modulation of parallel and complementary other systems. How this modulation is possible will be the topic of Sect.2.

Hippocampal trophism: neurobiology of aging and environmental factors

The hippocampus and its connections are a crucial neural structure for the topic of this work. In fact, talking about learning means also talking about memory. The hippocampus is involved in memory, location in space and time and the initial phase of action performance, so it is a truly relevant structure for the learning process. During life, as we saw earlier, our brain constantly changes its structure. Studying the neural features of age range allows us to highlight and reinforce the strong connection between synaptic changings and efficacy in learning performance. Many features characterized a lot of old subjects: decreasing of white and grey matter, hyper-activity of glial cells, changes in vascularization, decreasing of trophism of some brain areas, especially hippocampus. Alzheimer disease exhibits a dramatic volume loss in this area that is one of the most relevant roots of the symptoms.

The decrease in dimension of the brain in old age is due to three main factors: loss of neural cells, decrease of dendritic arborizations and reduction of dendritic spines. While changes in brain trophism are physiologically normal in the later stages of life, other factors can cause a decrease in hippocampal volume even earlier in life. We talked before about the role that some kind of hormones play during our life in brain activity.

Stress is one of the most relevant environmental factors in hormones balance. Under stressful conditions the structural problem that occurs in the hippocampus could be seen as similar to what happens in the age range case. Even though the primary cause is different, the process that leads to a decrease in synaptic arborization is more or less the same. In the hippocampus there are a huge number of glucocorticoid receptors. Under stressful conditions the number of these receptors sharply decreases, and so the hippocampus becomes unable to metabolize cortisol (McEwen, 1999). A considerable increase of cortisol levels, which is evident also in elderly people, determines problems in the synaptic arborization and, on the behavioral level, an evident worsening of learning abilities and memory performance. All these aspects of the change in neural

plasticity are well studied in post-traumatic stress disease (PTSD), and to shed light on these processes becomes relevant for treating patients successfully.

2 Neural plasticity and synchronicity

The importance of timing, particularly the study of synchronicity and coherence between neural activation sequences, appears to be crucial in advancing our understanding of brain function and subjective perception. In this context, I aim to explore the significance of synchronicity within neurophysiological research at the synaptic level. The first aspect of synchronicity relates to the timing of external stimuli, suggesting a strong connection between simultaneous environmental stimuli and the subsequent organization of neural activations in the brain. This concept is well illustrated by the Hebbian model.

Hebbian plasticity emphasizes the strengthening of synaptic connections through synchronized activity. The central principle of a Hebbian synapse is that neurons that fire together form stronger connections. The idea that synaptic changes driven by experience underlie associative learning dates back to the early development of the synapse concept itself (Cajal, 1894). Hebb's formulation of this hypothesis states that when a presynaptic neuron consistently contributes to the firing of a postsynaptic neuron, there is a lasting alteration that enhances both the quality and timing of the postsynaptic response. Here, when I talk about quality, I mean the coherence of the postsynaptic activation with the context and, when I talk about timing, I mean that there is a stronger sensibility in firing after a repeated signal under specific context conditions. In Hebbian synaptic structure, the activity in the presynaptic neuron becomes more likely to excite activity in the postsynaptic neuron, under specific conditions.

Martin et al. (2002) provide a comprehensive review of evidence supporting this hypothesis, which is widely endorsed by psychologists, cognitive scientists, and neuroscientists alike. The neurobiological process most commonly associated with Hebbian synapses is long-term potentiation (LTP). Recently, attention has shifted towards a variant of LTP known as spike-timing dependent plasticity (STDP) (see Caporale and Dan, 2008 for a review). In various neural networks, long-lasting changes in synaptic transmission occur by adjusting the timing between strong and weak synaptic inputs within a span of several milliseconds. The nature of this change critically depends on the relative strength of the inputs and their timing. Under certain conditions, transmission is enhanced, meaning that a presynaptic spike results in a "potentiated" postsynaptic response, characterized by increased amplitude or reduced latency. In other cases, transmission weakens, leading to a diminished postsynaptic response. Much of the research on LTP has focused on its cellular and molecular mechanisms. The relevance of this research to the neuroscience of learning lies in the hypothesis that connects LTP with associative learning and memory. Behavioral studies on the formation of associations based on interstimulus and intertrial intervals are heavily influenced by these timing parameters.

It is essential to understand what is meant by synchrony. From an external observer's perspective, stimuli may seem to occur at different speeds. However, perception is a highly complex and contentious issue, one example that might illustrate this complexity is about binaural beats (Ingendoh, R. M., 2023). Some theories suggest that perception is a reconstructive process, where the mind gathers various environmental inputs and

reassembles them into a coherent, meaningful reality. I will attempt to clarify the aspects of this issue that are pertinent to the goals of this work in the following section.

2.1 Plasticity through timing

In Sect.1 we explored a neurophysiological approach to learning, explaining it through the concept of neural plasticity. The focus was on morphological changes in the spatial structure of neurons, particularly through dendritic spines and synapse formation. This perspective emphasized the production, exchange, and metabolism of neurotransmitters, receptors, and the numerous molecules involved in modulating these processes. Thus, this explanation centers on the material alterations in neural connections at the cellular or molecular level. What we aim to focus on in this section is that informational changes determine the expression, retraction, and activity of dendritic spines. These structures modulate synapses, network plasticity, and the outcome of the learned output. The most decisive morphological aspect in learning processes seems to be related to synapses or, more precisely, to dendritic spines. In this section, we also suggest that the morphological structure of dendritic spines and their connectivity depend on informational variation, which is largely encoded at the level of the temporal architecture of signaling.

In this section, I present a new approach to understanding neural learning processes by focusing on information and its temporal structure. The core idea is that morphology of dendritic architectures is influenced by information encoded in neural spikes. In other words, learning occurs due to prior changes in the way information is coded and decoded by neural cells. The key shift is in how these cells process and transmit information to their connected counterparts. Recent studies in predictive coding framework suggest also a dendritic relevant role in processing prediction error signals. To address this, the authors connect predictive coding aspect of prediction error signaling to previous research on efficient coding in balanced networks with lateral inhibition and predictive computation in apical dendrites. Their work suggests an efficient implementation to the theory using spiking neurons, where prediction errors are computed locally within dendritic compartments rather than in separate units, Mikulasch & al. (2022).

A crucial factor in producing a learned response is a specific harmony between different neural regions or groups of neurons. Even the synchrony between a few neurons can be significant in interpreting how information is encoded. Here, the emphasis is not on spatial connections but on the patterns of neural activations and their temporal coherence. From this perspective, learning is best explained as a change in neural activity patterns. Therefore, to understand learning processes more thoroughly, we must examine the timing of neural pulses, either from individual neurons or groups of neurons. While we can observe neural activations using neurophysiological techniques, it is essential not only to identify which brain regions are active but also to study the rhythm of neural communication, its informational units, or, metaphorically, the "alphabet" of neural coding.

To comprehend learning, we must pay close attention to these changes in activation patterns. I will explore some key findings in this field to highlight the importance of timing, reframe learning processes from this perspective, and offer suggestions on how these processes can be enhanced. While I have previously discussed learning from a material, morphological, and informational standpoint, this section focuses primarily

on the role of time and timing in learning processes. A particularly relevant aspect of neural plasticity in this context is Spike Timing-Dependent Plasticity (STDP) and its influence on learning. In Sect. 1, I discussed Hebbian reinforcement, which refers to the strengthening of synaptic connections, but I did not address the time window in which this occurs. STDP ensures a causal interpretation of neural activations by considering the sequence in which neurons activate within a synaptic connection (a recurrent synapse).

For example, if two connected neurons activate and one is activated by an earlier stimulus, the synapse is strengthened in the direction starting from the neuron that responded to the first stimulus. This strengthening only occurs in one direction, not the reverse. This has been demonstrated in various studies and provides insight into how the brain interprets causality as a sequence of temporal activations. This explanation aligns with a different level of causality interpretation, such as the psychological perspective proposed by Hume (1746), in his opinion in fact, causality experience is only the experience of repeated connections in the time.

Another important point to consider is the short time window required for these synaptic connections to form, which is measured in milliseconds. If the interval exceeds a second, the connection loses its effectiveness. This observation leads us to another key issue, which is crucial for attributing identity and possibly for the sense of agency: the problem of size-distance invariance. Humans learn to identify objects despite changes in distance, size, or perspective. We propose that temporal contiguity plays a fundamental role in recognizing identity. Timing enables the subject to distinguish between different elements in the environment. When certain neural activation patterns consistently occur in close temporal proximity, the mind associates them into a meaningful whole. This proposal can be seen as an extension of the argument regarding the role of the body in perception. The synchronization factor thus appears to be fundamental for the conscious association between elements and events, which is crucial in learning processes, while also playing a key role in the morphological modification of synapses, particularly at the level of dendritic spines.

2.2 Plasticity and agency

Timing sequences might also explain the different perceptions of agency in various motor learning processes, whether voluntary (active) or afferent (passive), even though the neural changes are largely similar in both cases. When we examine the process of learning a motor action, neural changes occur due to neural plasticity, which can be explained by Hebbian learning and Spike-Timing-Dependent Plasticity (STDP).

In voluntary learning processes, individuals experience a strong sense of agency, while neural plasticity simultaneously modifies the brain, likely as a result of action repetition. However, significant changes in neural pathways can also occur during passive motor action reproduction, such as through the use of prosthetics, orthoses, or other devices. Some of these tools restrict the range of motion, thereby reinforcing neural networks associated with specific, effective movements (Pittaccio et al. 2017).

Other devices aim to facilitate learning by providing passive stimulation to specific body parts. It's important to note that, in both these cases, the subjective sense of agency is not as pronounced as it is in active learning.

Based on the neurophysiological, morphological, and temporal data reviewed in this study, we propose a timing-based explanation for the differing senses of agency associated with these two types of learning.

In voluntary learning, the underlying causal mechanisms seem to align with the principles of Spike-Timing-Dependent Plasticity (STDP). This model explains how the speed and efficiency of neural configurations associated with a particular motor task improve progressively with repeated practice. Through each repetition, the brain refines the timing of neuronal firing, making the neural circuits more adept at executing the task. The increase in efficiency is a direct consequence of this precise temporal coordination, which strengthens the connection between neurons involved in the motor action.

On the other hand, conditioned learning follows a different path. Although the end goal is still the production of a learned outcome, the subjective experience of control, or the sense of agency, may be diminished. This weakening of agency does not stem from alterations in the motor system itself, nor from spatial changes in neural connections. Instead, it appears to arise from differences in timing. More specifically, it may relate to how the internal timing mechanisms of the brain synchronize with one another. In conditioned learning, these variations in timing, particularly the coordination between distinct internal timing architectures, play a crucial role in shaping the learning process.

We aim to highlight the crucial role that timing dynamics play in the regulation specifically of dendritic spine behavior, including their expression, retraction, and overall activity. This timing dynamic could also help to understand the differences between various learning processes and the levels of agency perception connected to them. Dendritic spines are key mediators of synaptic transmission and plasticity determining the flexibility and adaptability of neural networks. These structures are not static; rather, they continuously respond to changes in informational flow, dynamically adjusting to optimize synaptic connections. This modulation of dendritic spines directly impacts network plasticity and shapes the output of learned behaviors, making them central to the mechanisms underlying learning. As said before, among the various morphological components involved in learning, dendritic spines emerge as particularly pivotal. While synapses in general are fundamental to neural communication, it is the morphological and functional properties of dendritic spines specifically that appear to exert the most significant influence on how learning is encoded and maintained at the cellular level. Their structural plasticity allows for the fine-tuning of synaptic strength, and this, in turn, contributes to the overall adaptability of the neural network.

Additionally, we propose that the morphology and connectivity of dendritic spines are closely tied to variations in information processing. These changes in spine structure and connectivity are not random but are highly dependent on informational signals. This informational modulation is largely governed by the temporal architecture of neural signaling, how signals are temporally coordinated and sequenced across the network. Temporal patterns in signaling play a key role in encoding information, and it is through this temporal framework that dendritic spines adapt, reorganizing themselves to support more efficient and precise synaptic transmission. In this context, the temporal organization of information serves as a driving force behind both the physical structure of dendritic spines and their functional integration within the neural circuitry.

3 Conclusions

The complexity of learning and cognitive development clearly emerges from the analysis of neural plasticity, a dynamic process that reflects the brain's ability to reorganize its synaptic connections in response to environmental stimuli. This study highlights how neural changes, from neuronal migration during embryonic development to learning processes in adulthood, are strongly influenced by genetic, epigenetic, and environmental factors. In particular, temporal factor and the synchronization of synaptic activations are critical for optimizing learning and memory formation. The concept of neural plasticity cannot be reduced to a mere structural remodeling; instead, it encompasses a wide range of functional processes that allow the brain to adapt to environmental changes.

The ability of the environment to influence the genome and, consequently, brain function, clearly demonstrates that learning is not solely a genetic process but rather the product of a complex interaction between heredity and lived experience. This is particularly evident in synaptic plasticity processes, where the temporal synchronization of activations plays a decisive role. The effectiveness of learning appears to depend not only on the intensity of the stimuli received but also on the temporal coherence between these stimuli and the corresponding neural responses. This research also highlights how adverse environmental factors, such as chronic stress, can impair brain function, particularly by negatively affecting hippocampal trophism and synaptic integrity. This underscores the importance of a favorable environmental context not only for facilitating learning and memory consolidation but also for preventing cognitive decline.

Moreover, the crucial role of temporal synchronization extends to our understanding of conscious perceptions of action and intentionality. The distinction between voluntary and conditioned learning can be explained not only by structural or functional differences in neural circuits but also by the distinct temporal patterns of synaptic activations. In this sense, the concept of temporal plasticity provides a new framework for interpreting the sense of agency that accompanies voluntary learning, suggesting that temporal coherence between external stimuli and internal neural responses is fundamental to the conscious perception of action.

Finally, the practical implications of these findings are numerous. Understanding the mechanisms of neural plasticity, particularly the role of time and synchronization, can offer new perspectives for education and cognitive rehabilitation. Interventions aimed at improving the temporal synchronization between environmental stimuli and synaptic modifications could enhance learning processes, especially in individuals with cognitive deficits or in rehabilitation contexts. Additionally, managing stress and creating favorable learning environments can reduce the risk of cognitive decline and improve psychological well-being.

In summary, this study demonstrates how neural plasticity is profoundly influenced by a combination of temporal, genetic, and environmental factors. Understanding the complex interaction between these elements not only broadens our knowledge of learning and memory processes but also opens new avenues for developing innovative therapeutic strategies in educational and clinical settings, with the aim of optimizing cognitive abilities and improving quality of life.

References

Cajal R. (1984), The neuron and the Glia Cell. Charles C Thomas Pub Ltd

Caporale N., Dan Y. (2008), Spike Timing–Dependent Plasticity: A Hebbian learning rule. Annual Review of Neuroscience 31 February, pp.25-46

Eccles C. J. (1994), How the Self Controls Its Brain. Springer

Eccles C. J., Popper K. (1977), The Self and Its Brain Springer, Berlino
trad. it. Giuseppe Mininni, Barbara Continenza - L'io e il suo cervello. Materia coscienza e cultura. Armando Editore, 1981 Vol 1

trad. it. Giuseppe Mininni, Barbara Continenza - L'io e il suo cervello. Strutture e funzioni cerebrali. Armando Editore, 1981 Vol 2

trad. it. Giuseppe Mininni, Barbara Continenza - L'io e il suo cervello. Dialoghi aperti tra Popper ed Eccles, Armando Editore, 1981 Vol 3

Edelman G. (1988), Neurobiology. An introduction to Molecular Embriology. Basic Books, New York

Edelman G., Mountcastle V.B. (1978), The Mindful Brain. Cortical Organization and the Group-Selective Theory of Higher Brain Function. MIT Press

Edelman G. (1987), Neural Darwinism. The Theory of Neuronal Group Selection. Basic Books, New York.

Hume D. (1748), An Enquiry Concerning Human Understanding

Ingendoh, R. M.; Posny, E. S.; Heine, A. (2023). "Binaural beats to entrain the brain? A systematic review of the effects of binaural beat stimulation on brain oscillatory activity, and the implications for psychological research and intervention". *PLOS ONE*. 18 (5)

Konorski J. (1948), Conditioned reflexes and neuron organization. Cambridge University Press

Larrabe M.G., Bronk D.J. (1947), Prolonged facilitation of synaptic excitation in sympathetic ganglia. Neurophysiology 10, March, pp.139-54.

Le Doux J. (2002), *Synaptic Self. How Our Brains Become Who We Are.* Penguin Putnam.

Livingston R.B. (1966), Brain mechanisms in conditioning and learning. Neurosciences Research Program Bulletin pp. 349-354

Lloyd D.P. (1949), Post-tetanic potentiation of responses of monosynaptic reflex pathways of the spinal cord. Physiology 33, pp.147-170.

Martin S.J. Morris R.G.M., (2002) New Life in an Old Idea: the synaptic plasticity and memory hypothesis revisited. Hippocampus 12 pp. 609-636

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, 22(1), 105-122.

Mikulasch, F. A., Rudelt, L., Wibral, M., & Priesemann, V. (2022). Dendritic predictive coding: A theory of cortical computation with spiking neurons. *arXiv preprint arXiv:2205.05303*.

Pittaccio S. & al. (2017), Passive ankle dorsiflexion by an automated device and the reactivity of the motor cortical network. 5th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)

Rose S.A. Handsaker R.E., Daly M.J., Carroll M.C. (2016), Schizophrenia risk from complex variation of complement component 4. Nature 530 pp. 177-183

Thompson R. F. Spencer W.A. (1966), Habituation: A model phenomenon for the study of neuronal substrates of behaviour. Psychological Review 73, pp.16-43.

Weaver, I. C. G., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., ... & Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, 7(8), 847-854.