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Subplate neurons: their biopsychosocial role in cognitive and neurodevelopmental disorders, nociception and stress

Abstract

A systematic review was carried out of the literature especially in humans reporting the origin, functions and neural changes of the subplate zone and the relationships with neurodevelopmental disorders and stress or nociceptive reaction in neonates. Thirty-two articles with established criteria were identified. Academic Google, SciElo, PubMed, Scopus, Cochraine Library and Web of Science databases were searched until January 2020 for scientific papers written in any language. Subplate neurons are present during embryogenesis of the nervous system and shortly after birth. Through them, the brain forms the first connections between the thalamus and the cortex originating sensory and cognitive capacities. Because of this, disorders involving migration and apoptosis failures or tissue injury can lead to psychiatric disorders, such as autism and schizophrenia, and to morphological alterations that may alter cognitive functions, modify the perception of pain in fetuses and neonates and have repercussions in adult life. Accumulative evidences reveal the importance of subplate neurons for neurodevelopment, previously ignored because they are transient cells. The elucidation of some morphological aspects of the cerebral cortex may explain mental disorders, the beginning of the perception of nociceptive stimuli and their implication in the long term.

Keywords: subplate neurons, neonate, nociception, stress, cognition, neurodevelopmental disorder

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Introduction

During embryonic development in mammals a primordial group of neurons forms as one of the earliest circuits to integrate the cortex, called subplate neurons (SPN), which play an important role for brain development and plasticity. Research aimed at understanding their functions is relatively recent, but studies have been carried out to clarify their implications for neuronal development, as well as the relationship between brain lesions and the origin of some cases of neurological disorders, namely autism and schizophrenia.[1] In addition, the better comprehension of the relationship between SPN-mediated connections and peripheral pathways may elucidate intricate questions about the origins of high-level mental functions and the roots for further disorders.

For instance, the origins of post-traumatic stress disorder symptoms in former premature children and adults may be possibly explained by the impact of stress reaction to nociceptive stimuli in the early brain, fetuses and neonates, and its other long-term effects. This mechanism is still poorly understood because it is unknown when the activity of a primary consciousness begins in humans. Despite this, it is believed that the trigger for pain sensitivity occurs ahead of other senses, early and gradually, and not due to a single initiating event.[1–3] It is known that for the perception of a painful stimulus it is necessary to have a connection between the nociceptors and the thalamic pathways and from there to the regions of the anterior insula, rotation of the anterior cingulate and prefrontal cortex. Thus, it is relevant to discover at what point in fetal development these structures are functional and communicating and which are related to alterations involving SPN and the later development of events such as mental or neuropathic pain disorders. These SPNs mechanisms may also include links to other disorders as mental retardation, autism and schizophrenia, as well as the intricate pathways to the perception of pain in newborns and during adulthood.[2–4]

Methods

The search for articles was conducted in January 2020 in six databases: Academic Google, PubMed, SciElo, Cochrane Library, Scopus and Web of Science. The keywords used in all databases were: "subplate neurons", "newborn or neonate and subplate neuron", "neurodevelopment disorder and subplate neurons", "cognition and subplate neurons", "stress and subplate neurons", "pain or nociception and subplate neurons", "Autism and subplate neurons", "Schizophrenia and subplate neurons". Each combination corresponded to an individual query. Keywords had to appear in the title or abstract. No restrictions were placed on language or year of publication. The inclusion criteria for this review covered original articles and review articles explaining the formation, functions, and changes related to the SPN. Exclusion criteria were studies that did not address SPN and cognition, neurodevelopmental disorder, mental retardation, autism, pain, nociception, schizophrenia or stress. Thus, 566 of the 623 previously chosen articles were excluded (Figure 1) mainly for reasons as animal study, only physiologic analyses, not newborn infant or other reasons as oral/poster presentation only. Reporting of the results followed the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) statement of 2009.

Results

What are the SPN?

The development of the human cortex is a complex and gradual process involving distinct cells and lasts for years after birth until it becomes fully functional. In general, it is possible to delineate three stages in cortical development: initial fetal circuit, transient and the cortical circuit (permanent).[5,6] During the formation of the telencephalon compartment, the subplate zone (SPZ), which characterizes the said transient circuit, is of substantial relevance, above all due to the performance of SPNs, which appear to contribute considerably to the maturation of this brain region by mediating various events.[1,4,6–9]

The SPZ is composed of migrating neurons, post-migratory neurons, glial cells, axons, dendrites and synapses, and is therefore composed of a reasonably heterogeneous cell population. The SPZ does not allow the use of a single molecular marker by fibrillary elements (axons, dendrites), as well as a vast extracellular space filled with a hydrophilic matrix.[6–8] The SPZ constitutes a wall in the fetal telencephalon and is extremely important both for structure and for intra- and extracortical connectivity.[8] SPNs are located at the white matter by permeating the cortical regions and allow synapse intensities to be lower than in the upper immature areas. They exist in an average number of 1.230 (+/- 549) in 1 mm^3 of the subcortical white matter with the lowest number consistently observed in the limbic cortex, and the highest number in the frontal cortex.[10] In the SPZ there are also neurons that secrete glutamate (projection neurons), GABA (interneurons that act locally), and neurons that are receptors for acetylcholine and glycine, as well as for the first two neurotransmitters cited. Clearly, the SPZ is a region of the fetus with the most complex of neurotransmitter systems. Because of this, it is inferred that internally the sub-square region makes a selection of the pulses that are transmitted, i.e., there is a register of received signals and works as a cortical amplifier with a role in the coordination of cortical activity.[1,6,7,11] SPZ has a sub lamination architecture in three 'floors' (deep, intermediate, superficial) from 15-21 gestational weeks with a stationary phase (22-28 weeks) and gradually remaining as a single layer in the newborn brain. Also, its internal characteristics are different from subjacent areas as low cell density, early differentiation of neurons and glia, plexiform arrangement of axons and dendrites, presence of synapses and a large amount of extracellular matrix.[6]

SPNs were first described from the fetal brain analysis of humans in 1974 by Kostović and Molliver and although SPN-related studies are relatively recent, authors argue over some hypotheses as to their origin in the evolutionary context.[12] Some believe that a common ancestor between mammals and sauropsids already possessed this zone; others believe that it is unique to mammals and is related to the brain growth of this group. Then there are those who admit the first hypothesis, but also affirm that some of these cells of the subplate are remnants of evolution due to known changes in brain development.[3,4,6,7] They have specific molecular markers, among them GABA, neuropeptide Y and somatostatin. They appear on the outermost part of the so-called mantle layer, the primordial region also called the pre-plate. Their first evidence came from nineteenth-century observations of cells called interstitial neurons, but their origin only began to be understood from the knowledge of the existence of the SPZ, which had harbored them previously.[7]

The initial fetal period, which corresponds approximately to the period between the 9th and 11th weeks of gestation, is characterized by the presence of cortical neurons that begin to migrate to the surface of the pia mater, forming a dense cortical plate. This, together with the marginal zone (above the first) and the zone of the pre-subplate (below it), form a trilaminar structure that constitutes the initial fetal cortex. As the neurons of these regions are only beginning their development, there are still no thalamo-cortical connections or even subplate performance, which only has the generation of spontaneous circuits and advanced morphological differentiation.[7,8] The SPZ begins to develop between 15 and 17 weeks of gestation, even when axons from the basal forebrain and thalamus are developing, which seems to be important for the analysis of intrauterine disturbances that may cause damage to cortical development. In this phase, synaptic and non-synaptic contacts occur between glutamatergic and GABAergic neurons, which together with the so-called Cajal-Retzius cells initiate functional activity in the cortex.[8]

At around halfway through the gestational period, the SPZ is already well developed, being four times thicker than the cortical zone and, therefore, capable of being responsible for the formation of synapses, with the presence of well-differentiated cells.[5,7] In this phase, the subplate receives the arrival of additional neurons, which is especially important for the development of the human brain, because it allows the installation of cells with varied types and forms. It is also here that the second class of interstitial neurons found in adults appears, which are located in the deep part of the periventricular white matter. Thus, as fetal development continues, the SPZ becomes the main post-synaptic target for all afferent systems in the cortex, receiving afferents from the basal forebrain, brainstem, thalamus, developing corpus callosum and other regions. Neural connectivity encompasses distinct developmental phases. Between the 24th and 25th weeks of gestation, a few neuronal extensions still enter the cortical plate, since most of the thalamic-cortical axons are in the waiting stage in the surface region of the subplate, a fact that characterizes the existence of a double circuit; thus, despite the arrival of fibers in the cortex, there is no data processing, and therefore there is no pain perception.[5] It is worth mentioning that the subplate reaches its peak of development between the 24th and 26th weeks, when it is constituted as the largest compartment of the telencephalon.[4]

From the 26th to the 28th weeks of gestation, thalamic-cortical axons begin to enter the somatosensory, visual, auditory and frontal cortex region, since they already project to the deep portion of the cortical plate, mainly in layers III and IV. At this time, SPNs act as transitory interneurons, since they perform the first thalamic-cortical activation.[5,6,8] Using real-time infrared spectroscopy, it was observed that from the 29th to 30th week sensorial functions are initiated, so there is already the sensation of pain, a fact that contributes to affirm the existence of a primary level of awareness at this stage of life. Between the 31st and 34th weeks there is a greater delimitation of the six cortical layers, but the subplate still remains a very significant layer; there is also the formation of primary grooves.[5] Between the 35th and 37th weeks, the occurrence of connections between the cerebral hemispheres is noticeable, which can be noticed by changes in electroencephalograms, since there is a significant increase in the number of axons in the corpus callosum, and these axons also penetrate the SPZ. From the 36th week to the end of gestation, there is long association pathway growth, and the subplate can still be visualized, namely by magnetic resonance after death, which demonstrates its importance for the development of these pathways. From this, it can be seen that even the term baby is born with circuits related to the fetal period.[5] Therefore, there is a moment of coexistence of two neural circuits: the transient, characterized by the functions allowed by the

SPZ, and the cortical, characterized by complex connections that are slowly formed and will remain throughout life.[4]

Some cortico-cortical fibers begin to develop in the first few weeks after conception, while others take up to three years postnatal to become adults.[4] Cortical deep projection neurons in the caudal fetal cortex appear to exclusively derive from SPNs, though a study modeling subplate formation with human pluripotent stem cells (hPSCs), showed that all classes of cortical DPNs can be specified from SPNs.[13] The pathways of association in the SPZ are developed after the 30th week of gestation, which makes the presence of this zone significant during this window of cortical development.[4] In animal models, a study showed that SPz respond to sensory auditory stimulation in ferrets with a electrophysiological nascent topographic organization emerging before the onset of spiking responses in layer 4 indicating that early sensory experience can activate, modulate and potentially sculp subplate circuits.[14] This synaptogenic scenario is the basis for a variety of early electrophysiological and behavioral phenomena in fetuses and preterm infants. It is also worth noting that the SPZ is not uniform, with differences in the extent of the area occupied by it in the frontal and occipital regions, the latter being somewhat larger.[4] The analysis of fetal cortex magnetic resonance, both in vitro and in vivo, allows observers to identify the SPZ with reasonable facility because of the large hydrophilic extracellular matrix space. This is particularly noticeable between the 17th and the 30th weeks of gestation, since this is the period of greatest volume, especially the region of the prefrontal cortex, in this way, the subplate normality of cortical development. Importantly, during the period when there is an intense increase in the SPZ that this zone stands out as a waiting station for cortical afferents, as there is also significant growth of thalamic-cortical afferents, which may reside in this area until the 26th gestational week. This growth is made possible by the subplate cell matrix which, in addition to a significant number of axon-orientation molecules, also has proteoglycans.[5,6,8]

As the white matter is formed, the SPZ is eliminated by apoptosis, since it is a transient fetal compartment; however, most of the SPNs remain and become part of the region in which they are located, acting as interstitial neurons. This is also due to the reorganization of the architecture of the postnatal nerve fibers, mainly due to the development of twists, grooves and white matter, which destabilize and lead to the disappearance of SPZ.[4,8] These surviving neurons undergo changes in adaptive morphologies, besides changing in number and positioning within the forming cortex, which can generate changes in cortical circuit functioning. Little is known about the functions of these neurons, but, in general, they are known to act as interneurons that modulate the presynaptic entry of different cortical afferents, such as brainstem and thalamus.[6,8]

They are present in a greater proportion in mammals, such as cats and humans, a fact that suggests a greater need of these animals to perform more complex and imbricated tasks where more cortical regions are involved. In humans, in particular, there is a greater number of SPNs as well as an increase in their different types, arrangements and distribution in the telencephalon. Because there are no similar cells in other points of the nervous system, such neurons appear to be related exclusively to the maturation of the cortex region. In general, the SPNs act as guides for neural connection and reconnection, and as they are eliminated they ensure that the plasticity in the critical period, which will be punctuated later, occurs only once so that more complex activities can be implemented in the future, with the initial stretches matured.

In summary, it is known that at the beginning of fetal life, the thalamic axons are not yet fully developed and, therefore, do not project to cortical areas, since they are short. In this situation, early neurons below the cortical plate receive the thalamic afferences from glutamatergic (excitatory) stimuli and perform synapses with the cortical neurons, especially for the IV layer. As the thalamus matures, the SPZ is eliminated by apoptosis and the thalamic axons already perform direct synapses with the cortical ones, although synapses persist with SPNs; this is the so-called critical period, when different connections are being reconfigured while distinct sensory experiences are occurring. In the adult, these SPNs barely exist with the same functions, and the thalamus assumes the role of transmitting information to the cortex. Such findings are related to experiments performed, for example, with cats, from the observation of neuronal latency by stimulating the white matter of the visual cortex. The first observations were performed shortly after birth, and low latency was observed in the SPZ and high latency in the cortical (layer IV). Over time, new tests indicated low latency in the cortical area, indicating maturation of thalamic-cortical connections.[1]

Functions performed by SPNs

Among the objectives in elucidating the roles of SPNs, analyzing them as an important transient circuit, new studies have been proposed to understand the relevance of these cells for proper cortical functioning, as well as for the occurrence of neurological disorders associated with deficits in connectivity.[8] Tests performed with newborn rodents revealed that the resting membrane potential of these cells is -55mV. The properties related to voltage, sodium current dependent potentials and action potential are fully functioning, and this allows the adequate transmission to the cortical neurons, promoting their development. The subplate is important for acting on the generation of oscillations in cholinergic neurons, as was perceived from experiments performed with newborn rodents; however, it is necessary that the region is intact. It has been proposed that the SPZ is capable of acting as a pacemaker and thus of generating waves for the developing cortical region. These oscillations lead to the release of the Brain Derived Neurotrophic Factor (BNDF), which is associated with the strengthening of synaptic connections in this period of maturation; the oscillations also influence the occurrence of apoptosis, since they activate the TrkB BNDF receptor. The performance of this region also interferes in the pattern of neuronal migration from the release of neurotransmitters from glutamatergic and GABAergic neurons, and this secretion is greatly increased with the increase of oscillations in the area. Subplate ablation or even loss of integrity interrupts the generation of oscillatory waves and compromises the cortical architecture in columns, relevant for the formation, for instance, of the visual cortex. SPNs are also associated with the targeting of the thalamic axon fibers to a particular area in the cortex. In the critical period, when ablation of this area begins, the thalamus neurons grow, taking over the path around the area where the subplate was removed and thus reach a target in the IV layer where those SPNs acted. In other words, there is a previous road, which makes it possible to maintain routes. In addition, it is the fact that synapses are already strongly established between SPN and the IV layer that helps in strengthening the newly formed appropriate thalamo-cortical connections, facilitating the development of thalamic projections; the process resembles the drafting of an outline that is then available for the subsequent construction of definitive transit routes. Authors propose that the strengthening of synapses is linked to potentiation or depression of these in the long term, which characterizes synaptic

plasticity. Such potentiation, however, requires the synapse to have the level necessary to modify the intracellular environment of the postsynaptic neuron; if this synapse is not capable of acting alone it is possible that more than one synapse occurs simultaneously, one being strong enough, a process called associative potentiation. This is the mode of strengthening generated by SPNs in the thalamic projections that begin to interact with the cortical neurons from the critical period. Because the synapses between the thalamus and the cortex are initially weak, that is, they take longer to stimulate the neurons in the cortex, the SPNs are the cells that trigger and activate the cortical area. This delay of the thalamus, however, allows the long-term potentiation, and these synapses are gradually strengthened and maintained, as the subplate is ablated.[1] Hence, SPNs feed-forward circuit may build the formation and plasticity of thalamocortical connections that is also a two-way path as also receive inputs from the developing cortical plate and project to the thalamus.[15]

Another very important event for proper cortical functioning is the maturation of inhibitory impulses, which is related to the occurrence of sensory stimuli. Because the SPNs strengthen the connections with the cortical region, the transmission of sensory impulses is ensured and thus the inhibitory maturation is well observed. This maturation is linked to the development of chlorine homeostasis and the maturation of the GABAA receptor. It has been realized that withdrawal of the subplate reduces this inhibition because of the reduction of the levels of KCC2, a Cl- transporter, and the maturation of the cited receptor.[1] Still immature GABAergic neurons act initially on the depolarization of other cells (excitatory stimulus), since there is a low expression of molecules like KCC2, controlling the level of this ion in the neuronal cytoplasm. In normal conditions, over time, the amount of KCC2 increases, with an outflow of Cl-, which makes the equilibrium potential more negative than the rest, leading to the entry of Cl- back into the cell and a consequent hyperpolarization of the neuron, a function that persists throughout life, a fact that triggers an inhibition response to the stimulus. Such a function of the SPNs has been demonstrated when it is realized that the removal of this neuronal group compromises the formation of these neurons of inhibition. In addition, subplate extraction may also lead to the persistence of these GABAergic neurons as depolarizing, because of the blockade of glutamate signaling to the IV layer, a situation that apparently correlates with the hyperpolarization of these neurons, since they appear to be the main contributors to excitation via glutamate in the cortex. Thus, early SPN ablation may generate hyper-excitability in the brain, which may justify the occurrence of neurological disorders. The occurrence of inhibitory maturation also appears to be associated with plasticity during the critical developmental period. Therefore, removal of the subplate also interferes with the proper remodeling of cortical connections, as it interferes with plasticity after this stage.[1] The cortical inputs to SPNs in early ages are mediated by N-methyl-D-aspartate (NMDA)-receptor only.[15]

The presence of SPNs is also important for cortical responses to establish, persist and obtain a pattern of organization of the nerve fibers, although the thalamic projections have already reached the cortex region. In the experiments performed in the visual cortex of cats, the removal of the subplate allowed visual perception faults to be observed with a lower degree of refinement. In the aforementioned experiment, when performing monocular deprivation with previous ablation of the subplate, contradictory remodeling occurs. Instead of forming more prominent ocular dominance columns in the areas corresponding to the open eye, there is not only removal of thalamic-cortical projections in the region in which the eye was closed (deprivation of sensorial stimulus), but also in the region that represents the active eye.[1] It has been proposed and proven that SPNs have a significant role as a secretory protein, possibly associated with their role in cortical maturation, a fact associated with the observation of a notable amount of rough endoplasmic reticulum, an important organelle for protein synthesis. The observation was successful in rodent brains at P8, where a large amount of Nissl substance was observed in the SPN cytoplasm, in addition to a morphology very similar to that of other essentially secretory cells such as plasma; this substance corresponds to a basophilic granular area, which refers to the presence of the rough endoplasmic reticulum. It was also observed that endoplasmic reticulum stress occurs in these cells, an event that characterizes secretory cells due to the high expression of proteins, a fact that can be evidenced by the high amount of BiP–an immunoglobulin heavy chain binding protein whose expression is related to stress conditions such as hypoxia or lack of glucose.[9]

Recently, some authors have also postulated that the existence of SPN in humans, due to the greater variety and quantity in this species, is co-responsible for the larger and more complex brain development, credited to evolution. At the same time, decisive changes take place in the pattern and organization of the life allowed for energy and metabolic increases, a process called reserve capacity. Due to changes in feeding, reproduction and extensive care of the offspring, neuronal development and plasticity occur gradually, which allocates more time to the maturation of the cortex while the SPNs perform intense synapses and interconnect different regions, including in the perinatal period. This additional time in comparison to other primates, for example, enabled the improvement of cognitive abilities, learning, language, self-awareness, as well as better recovery after cerebral lesions.[6,8] It is worth mentioning that the continuation of SPN presence, due to faults in apoptosis mechanisms, interferes in the adequate establishment of the cortical connections in the adult. This event is related to the manifestation of disorders, which will later be disrupted, since such persistence is associated with abnormal circuits, pathologies and neurological dysfunctions.

Neurodevelopmental Disorders linked to SPN

Autism

Autistic Spectrum Disorder (ASD) encompasses a set of characteristics that include deficits in social interaction, development of delayed or absent language, and repetitive and restricted behaviors. There is no single biological marker that is determinant for the characterization of this disorder.[14–16] The spacing between neurons, disturbances in the pattern of organization, and irregularity in the borderline between the white and the gray matter of the brain are typical morphological changes found in the cortex of people with Autism Spectrum Disorder (ASD). The lower distinction between white and gray matter in individuals with ASD is due to the presence of supernumerary neurons that have failed the apoptosis process or presented a migration deficit in the SPZ. In addition, factors such as calcium signaling, gene expression and neurochemical changes may interfere with neural modeling and the development of cortex layers.[17] Studies in rats have shown the influence of valproic acid (VPA) on ASD, especially when this substance, considered as an anticonvulsant, is too present in the genesis of SPNs. This exposure generates faults in the maturation of the cortical circuit trajectory, contributing to the alterations of sensorial stimuli. In addition, it acts on the inhibitory and excitatory balance of SPN, GABAergic and glutamatergic

circuits, causing hyper-connectivity in these sites, which culminates in the onset of the central symptoms of the disorder (hearing failure, behavior and communication). In addition, it was found that the presence of VPA modifies the number of transient neurons surviving after birth.[16]

Contributing to the factors related to the genesis of ASD, it is important to highlight the expression of certain dynamic SPN genes that reveal a close relationship with the onset of autism spectrum disorder and schizophrenia. Associated with autism are the Atp6a2, Cadps2, Cdh10, Cdh18, Cdh9, Gabra5, Nrxn1, Plp1, Prss12, Sema5a and Tppp genes. Of these, five are specific to the SPZ. As autism usually begins at the preschool age, it is understandable that this disorder is associated with genes that play a role during development.[18]

Schizophrenia

Schizophrenia is a disease that covers about 1% of the population and affects mostly men. Among the symptoms of this pathology are: strange behavior, social alienation, bizarre ideas or feelings of persecution, the act of speaking alone, among others. This disorder has been related to prenatal disorders in the SPZ where transient neurons form cortical circuits essential for this phase.[7,19,20] The heritability of this pathology is about 80%, which confirms the strong genetic character of the disease. However, environmental factors also contribute to the development of the disorder, which corroborates the abnormal development of the prefrontal cortex whose function incorporates cognitive and behavioral mechanisms. SPNs may be key components in the pathogenesis of the disorder, since they form the first neocortical circuits.[6,8,21,22] It is worth mentioning that the SPNs are the first in the neocortex to perform a connective function between the cortex and the thalamus beyond cortical development. The increase of GABAergic neurons promotes an inhibitory barrier in the prefrontal neural circuit. In this way, there is a failure in the connection and modulation of the limbic system and prefrontal cortex.[8,23]

The number of surviving SPNs and the change in them may be involved with the incidence of some types of schizophrenia, though their role in the pathogenesis of schizophrenia is yet unknown.[23] Through the use of monoclonal antibodies against proteins present in the SPN microtubule (MAP-2) it is possible to quantify the surviving neural density in the post-frontal and pre-frontal white matter.[21] It has been found that the amount of MAP-2 was higher on the cortical surface in individuals with the disorder. However, the amount of neurons in the white matter decreased by depth in both normal and pathological brains. It is also worth mentioning that neurons containing nicosamide-adenine phosphate-diaphorase (NAPHd) dinucleotides showed a greater distribution in deep regions of the white matter in brains that had the disorder.[21] It is noteworthy that in 35% of cases of schizophrenia changes are observed in the SPZ, which is understandable due to the diversity of symptoms of this disorder. Thus, it is important to note that SPNs are not solely responsible for schizophrenia.[8]

Cognitive impairment

Different factors are associated to cognitive impairment or mental retardation. Among them, the neonatal hypoxia is a condition that leads to sedation of neurons from the rise of white, subcortical and SPN surfaces that will become vulnerable when exposed to excitotoxicity.[20] This situation is one of the main causes of periventricular leukomalacea (PVL), in which a multifocal necrosis is an underestimate that may be responsible for an abnormal growth of the brain, culminating in cerebral palsy and mental retardation or intellectual deficiency.[24] Peak upper two SPN coincide with gestational age associated with LPV. The excessive death of SPNs can be associated with visual impairment, since these neurons form an important visual pathway, as the connections between the cortex and the thalamus culminate in important sensory, auditory and visual pathways. Survival mechanisms of SPN are not yet fully understood; however, it is known that early cell maturation, increased glutamate receptors including the NMDA 1 receptor and AMPA are closely related to the vulnerability of these cells.[24] Despite the effects of neonatal hypoxia, it is known that the neuroplasticity of a fetus's brain is greater than that of an adult. In addition, the tendency of prenatal neurons to undergo hypoxia is less than the same cells in an adult brain.[25] Although there are studies in this area, it is still not entirely clear whether changes in connectivity may influence the survival of some SPNs. However, it is accepted that when an injury occurs in the SPNs, the thalamic axons cannot recognize their target in the appropriate cortex and reach the normal connection pattern.[18,25] Studies referring to the cortex suggest that in the presence of injury in this region there is a migration of germ-zone neurons through the white matter, reaching the part of the cortex that is suffering injury resulting from hypoxia or inflammatory processes.[26,27]

Prematurity is another important cause of cognitive deficits. Term children who undergo evaluation tests years after birth perform better in cognition, attention, and executive function than children who were born preterm. Prematurity also may alter the maturation patter as measured in a study that compared premature and full-terms by equivalent age using 3T MRI T2-weighted and showed that the majority of transient fetal compartments were less mature in preterm group at term equivalent age, though von Monakow segments of the white matter and subplate compartment presented a more advanced maturational stage in the preterm group compared to the term group.[28] These differences are still to be investigated at long term. Because they are the first neural cells to mature, SPNs are the most vulnerable cells to hypoxia-ischemic processes common in prematures.[24,26] In addition, there is an increased risk of preterm infants developing cerebral palsy and psychiatric illness.[26]

Moreover, evidences comes also from congenital hypothyroidism and early exposure to alcohol in the fetal alcohol spectrum disorders (FASD) especially at the third trimester of pregnancy. Congenital hypothyroidism leads to pyramidal neurons apoptosis associated to upregulation of p75 NTR that are confined to supragranular neurons. FASD mainly affects the third trimester, which is characterized by intense synaptogenesis and the alcohol-induced apoptosis of infragranular layers and this is thought to be caused by the simultaneous blockade of NMDA receptors and activation of GABA receptor. Different types of intellectual deficiency presents an unbalanced weights of supra- and infragranular layers and can be associated to sensory and memory processing deficits.[29] The role of SPNs and its modulating function over the pyramidal layers and the impact of these congenital conditions need to be clarified. These findings demonstrate the importance of good neural development of the nervous system, especially of the cerebral cortex, which represents an area susceptible to injury and alteration during neocortical maturation.[26]

Development of the fetal nervous system and nociception

The first structures of the fetal nervous system that begin to develop and connect via synapses are those of the periphery and spinal cord, which in sequence will communicate with the thalamus, later with the SPZ and finally with the cortical regions. Thus, nociceptors are initially formed in the perioral area around the seventh week of

gestation, and also form in the face, hands and surface of the feet around the second week. Thus, by around the 12th week reflexes already occur due to the connection to the spinal cord, without any cortical involvement. At the end of 20 weeks, these nociceptors will be present throughout the skin and mucous membranes, and the synapses will now occur through their stimulation.[2,29] It is from the 17th week that thalamic pathways project to the SPZ, and it is only after this stage that the afferent reaches the critical points of its interpretation, although it is not known exactly when the nociceptive fibers are routed to this region. From some studies, however, it is believed that the perception of pain begins around the 20th week, but still weakly, and is actually functioning around the 26th week. In addition to anatomical observations, from clinical practice with preterm infants it was noticed that between the 24th and 26th weeks the nociceptive pathways are active, but the specific period of this maturation is not known. It is worth emphasizing the possibility that fetuses feel pain more intensely than adults, because it is around the 27th-28th week of gestation in humans that the onset of inhibition begins.[2]

Nociception can be assessed by observing the behavior of the fetus by ultrasound or by variations in heart rate. In studies conducted by Vivette Glover and Nicholas Fisk the stress response can already be analyzed via the serum level at the 18th week of gestational age, in which high values of cortisol and β-endorphin were found after intrahepatic vein intrauterine transfusion.[2] As the procedure was extended, the serum levels of these substances were higher, and this result is independent of the maternal response; in addition, these values increase as the gestation continues. Such findings indicate the maturity of the hypothalamic-pituitary-adrenal axis (HPA) by the middle of gestation and can be used as parameters to evaluate the degree of lesion in tissues and as markers for analgesia or anesthesia. In addition, by means of ultrasound, a change in blood flow was observed as a response to chronic stress caused by restriction of growth around the 16th week; there was increased circulation to essential organs such as the heart, brain, and adrenal glands at the expense of peripheral circulation.[2]

Fetal responses to stress

Perinatal stress has been mainly studied in animal models. It is known that in the neonatal period, which is fundamental for the development of the nervous system, fetal reprogramming may occur due to stressors (physical, nutritional, hormonal and exogenous, in the form of drugs), which may leave the neonate prone to behavioral changes, alterations in memory and psychomotor development, as well as personality, cognitive, anxiety and psychotic disorders in childhood and adulthood.[30,31] Among the main structures affected in the neonate due to this factor are: HPA axis, glutamatergic, serotonergic and GABAergic systems, structures (prefrontal, temporal and insular cortex), subcortical structures (amygdala and hippocampus), cerebellum and placenta. Studies on maternal stress during pregnancy corroborate the idea that stress in this phase may act as a teratogen agent, primarily in the early stages of pregnancy. The consequences of this factor can range from a simple reduction in the level of uterine sites for implantation of the blastocyst to prematurity, low birth weight and abortion.[31]

With the implementation of neonatal intensive care units, the survival of preterm infants has increased considerably. In addition, environments in which babies are subjected to constant lighting and procedures perceived as painful, as well as instability of body temperature, weight loss and stress, have provided a research front regarding the quality of sleep in babies and their future considerations. Sleep is a predominant state in the life of the newborn, because during this period there is maturation of the nervous system, memory consolidation, and synthesis of protein and growth hormone. The method of the kangaroo position in neonatal intensive care unit has been shown to be a great advance in trying to maintain body temperature and decrease respiratory effort by increasing sleep levels. Studies indicate that about 15% of premature infants present severe or moderate brain damage and about 50% require specialized follow-up during childhood and adulthood. Changes in neurodevelopment occur mainly at the end of the second and third trimesters. In this period the development of the cortex, subcortical region and neurons of the frontal lobe have not yet organized, what turns this population of greater risk for neurodevelopment as SPNs functions are challenged and enhances the relevance for follow-up studies.[31,32]

Final remarks

The current findings concerning SPNs converge in strong evidence of the SPNs' role in the structure and functionality of the neocortex. It has been investigated the possible link to disorders of difficult psychopathological explanation as autism and schizophrenia. This review also discussed the SPNs' role at the impact into adult life of early exposition of fetuses and newborn infants to stress or nociceptive stimuli. Methods such as magnetic resonance imaging and biological markers aid in the identification and analysis of circuits that can elucidate unusual patterns in the brains affected by premature birth, gestational and neonatal stress and some disorders such as cognitive deficits, schizophrenia and autism. These conditions refer to morpho-functional characteristics that fall directly into the site where SPNs are established. In autism, the distribution pattern of the white and gray matter of the brain is not as obvious as in normal brains. In schizophrenia, the abnormal patterns of the structure of the prefrontal cortex are revealed since the prenatal period, as they affect the first neurons to establish synapses in the neocortex. It is possible to question if the inherited mature thalamic oscillations would be altered in neurodevelopment disorders. For instance, one study found low peak frequency of motor-related gamma oscillations from the contralateral primary motor cortex, peak frequency of 74.36 *vs*. 80.47Hz, comparing children with autism and typical development respectively, with lower power as well for the group with autism.[33] These findings were associated with the severity of autism symptoms, though studies tracing the evolution since early ages are necessary. In addition to these psychopathologies, other abnormal patterns of cortical impairment may influence the involvement of normal brain functions, such as neonatal hypoxia-ischemia and its relation to intellectual deficits. These neurons also appear to be related to the onset of painful stimuli perception in intrauterine life, and perinatal stress should be perceived and reduced in function of the repercussions for the quality and life expectancy of the adult. Thus, the studies responsible for the recent discoveries reveal the importance of the study of SPNs, which had been too long ignored, as they were considered transient cells.

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Conflicts of interest

The authors declare no conflicts of interest.

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