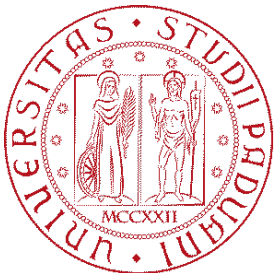

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Development of brain structures following perinatal cerebral lesions suggests the involvement of the cerebellum in the working memory network

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ABSTRACT

Crossed cerebro-cerebellar diaschisis in very preterm born individuals, following perinatal cerebral lesions, reveals functional connectivity between some cerebral areas involved in working memory (WM) and yet undefined cerebellar regions: this may support the role of the latter in the WM network. The cerebellum has long been associated with motor control and coordination. In the last two decades, researchers have studied its involvement in a broad range of cognitive functions, such as visuospatial attention and WM. In this overview, I define the brain regions activated by the WM network and their development in term- and very preterm- infants compared, according to the most recent studies. These findings could contribute to support the involvement of the cerebellum in non-motor functions, specifically in WM.

1. WORKING MEMORY FROM THE PSYCHOLOGICAL AND NEUROSCIENCES PERSPECTIVES

1.1. Psychological perspective

The concept of working memory (WM) refers to the brain system that provides temporary storage and manipulation of information. WM enables us to perform complex cognitive functions, such as language comprehension, learning, and reasoning (1). The notion of WM is closely linked to that of short-term memory (STM). Even if they are often used interchangeably, the latter is responsible for the mere maintenance of information, while WM is extensively involved in goal-directed behaviors in which information must be retained and manipulated to ensure successful task execution (2).

Since the term *working memory* was first introduced by Miller in 1960 (3), several theories have been proposed contributing to the memory field, which is currently in constant expansion. One of the most influential WM theories is the multiple-component model proposed by Baddeley and Hitch (4). According to Baddeley, WM consists of three modality-specific subcomponents: the central executive, the phonological loop, and the visuospatial sketchpad. The central executive is the main system in charge of directing and dividing attention during tasks, responsible for the coordination and integration of information coming from the long-term memory (LTM) and the other two subcomponents, considered as slave systems. The phonological loop represents the evolution of the basic speech perception and production systems, responsible for storing information by continuously updating it in a rehearsal loop. It is subdivided into the phonological store, which holds acoustic or speech-based information we hear for 1 to 2 seconds; and the articulatory control process, which allows us to repeat verbal information in a loop, somewhat analogous to inner speech. The visuospatial sketchpad is related to the process of perception and action and is in charge of the storage of visual and spatial information. It allows us to keep track of where we are in relation to other objects, as we move through the environment (1). Later, Baddeley extended the model by adding a fourth subcomponent: the episodic buffer (5), a multi-modal store capable of holding sensory pieces of information, sourced by perception and the other two subsystems, and binding them together into unitary episodic representations linked to the central executive. It also seems to play a crucial role in conscious awareness.

In 1999, Cowan proposed an alternative conception of WM: the embedded-processes model (6). In this view, WM refers to a set of cognitive processes that retain information in an easily accessible state. The term ‘embedded’ recalls the hierarchical relationship between its components: long-term memory (LTM), the subset of long-term memory in a temporarily heightened state of activation, and the subset of activated memory in the current focus of attention and conscious awareness. The latter is assumed to be controlled by a unitary central executive, named the supervisory attention system. Cowan describes the focus of attention as capacity limited, a much-debated topic in the WM research field.

There’s a strong correlation (r = .97) between working memory capacity (WMC) and the efficiency of its central executive component (7), which is accountable for the coordination of multiple cognitive functions, such as attention, cognitive flexibility, cognitive inhibition, and others, particularly under conditions of interference or distraction. The key role of WMC in predicting executive and cognitive performance is supported by plenty of evidence. In 1969, Pascual-Leone postulated that STM capacity increases steadily throughout childhood, along with Piagetian developmental stages, which underlie improvement in cognition (8). Another study that investigates memory across the adult lifespan, suggests that aging leads to a decline in WM performance and capacity (9).

1.2. Neurosciences perspective

Following the theoretical formulation of working memory models, numerous studies investigated the brain areas related to WM, integrating data from various research methods such as single unit recordings in monkeys, the cognitive performance of human neurological patients with focal lesions, and brain imaging techniques. This allows us to have an overview of the WM network and its neural basis, even if this research field is still open and incomplete.

1.2.1. Cerebrum

The prefrontal cortex (PFC) is surely one of the most interesting and not yet completely understood portions of the brain. PFC is thought to be the most important substrate for WM. Evidence of the involvement of this brain area in the WM network comes from the early 20s when Jacobsen tested primates with lesions involving the PFC area and found performance deficits (10). The submitted

test was the delayed response trial, in which the subject observes food concealment under one of two identical cups and, after a variable delay, is allowed to choose the right one. The temporal delay between cue and response is the key element in making this trial useful in the study of short-term memory because it's necessary to recall the recent experience of seeing the food being placed under the cup. Later, in the 70s Fuster recorded the neuronal activity in the PFC of monkeys using a micro electrodes system, while the primates were performing the delayed response task (11). He reported persistent and sustained levels of neuronal firing during the entire length of the retention interval, proving the role of the PFC in processes of sensorial and mnemonic attention.

The results of recent functional neuroimaging studies with human subjects are consistent with the above evidence and provide further findings. For example, it has been emphasized the role of the dorsolateral prefrontal cortex (DLPFC) in facilitating the maintenance of information. The maintenance process can be divided into selection and rehearsal and the DLPFC seems to be involved in both (12). The selection of responses consists in managing information to be rehearsed and in the recruitment of posterior regions that can maintain active information to be remembered (13). On the other hand, rehearsal is an operation that supports WM by reactivating or refreshing transiently stored representations. The DLPFC, in this view, does not store representations of past sensory events itself. Instead, its activation is an extra-mnemonic source of top-down control over posterior regions that store the representations. The repetitive focusing of attention on the items to be remembered is rehearsed, refreshed, and bolstered against degradation and distraction. All of these scenarios, although different in kind, could lead to explaining the persistent activity that has been observed during retention intervals of WM tasks. From this point of view, the DLPFC seems to play the role of the central executive from Baddeley's theory.

In another interesting fMRI study, Chobok Kim et al. have compared the activation of DLPFC to the activation of the frontopolar cortex (FPC) during the manipulation of integrated information in WM. They designed a task consisting of a complex manipulation condition (CM), where participants were required to manipulate two features of an integrated item, and a simple task (SM) with only one feature of an item. The results showed the same activation of FPC in both CM and SM conditions. A delay was recorded in the CM relative to the SM, consistent with the fact that encoding complex stimuli require a longer time to successfully maintain representations than simple stimuli did. In contrast, DLPFC appeared to be more sensitive to task complexity: it recorded greater activity in the CM than in the SM. These findings suggest that FPC is involved in the production and in manipulation of integrated information held in WM, whereas DLPFC appears to be more involved

in manipulation processing demands (14). They are both crucial for complex cognitive tasks, such as reasoning and planning. In this view, FPC seems to mirror the role of the episodic buffer from Baddeley's model: to bind different types of information, visuospatial and phonological, into a single episodic WM representation. The function of the prefrontal cortex in WM remains in part unclear. It now seems that PFC is not only required during the maintenance of information but also during other phases such as encoding and retrieval (15).

From what has been said, the anterior regions of the PFC cover a supra modal control role, it is in charge of selecting responses, directing attention, and refreshing stored information. This stored information seems to be maintained in modality-specific sensory areas in the posterior cortex. For example, it has been established that verbal and acoustic information activates Broca's (44BA) and Wernicke's (22BA) areas, while visuospatial information is located in the occipital lobe, in accordance with the division of visual-spatial and phonological buffers in Baddeley's model (16). The neural basis of visual processing constitutes two different pathways: one proceeds ventrally, interconnecting the striate, prestriate, and inferior temporal areas, and enables the visual identification of objects, like their color and shape. The other runs dorsally, interconnecting the striate, prestriate, and inferior parietal areas, and allows instead the visual location of objects (17). These and other key findings included sensory areas as short-term stores for sensory information in the WM network (18).

An fMRI study tested activation in prefrontal, temporal, and anterior cingulate cortex (ACC) areas while the subjects were engaged in a listening span test (LST) condition, which required to remember the first word of each sentence while concurrently judging whether each sentence was semantically true or false. It was found a great activation in the dorsal site of the ACC, which seems then to be involved in attention control such as dividing attention and monitoring task performance (19).

Further investigation has recently revealed that basal ganglia, a group of subcortical structures, play a crucial role in the WM network too (20). Findings show that the bilateral caudate and thalamus are engaged in the encoding phase of a WM task, while the bilateral medial thalamus and posterior cingulate regions are implicated in the maintenance phase of the task. During the retrieval phase activity comes from the left inferior frontal sulcus and posterior parietal and occipital regions.

1.2.2. Cerebellum

As discussed below, WM tasks appear to activate structures other than the cerebral cortex. There is increasing evidence that underlies the contribution of the cerebellum to higher cognitive functions, that transcend motor control. This view is supported by the fact that the cerebellum contains more than half of all the neurons in the whole brain (21). The cerebellum is strongly interconnected with the contralateral higher-order cerebral areas, including the DLPFC, as well as the parietal and superior temporal areas.

In a 2004 study (22), 21 patients with focal cerebellar lesions were assessed through a neuropsychological test battery, which examined memory (WMS-R), attention (TAP), executive functions (WAIS-R, MCST, K-ABC, COWAT), motor functions (Purdue Pegboard Test), and others. Patients showed significant impairment in general memory, delayed recall, visual memory, logical memory, and visual reproduction. Higher attentional functions such as divided attention appeared to be compromised too. In general, since these cognitive impairments cannot be explained by motor disabilities, these findings support the idea of dysmetria of thought resulting from cerebellar lesions. Dysmetria of thought is the concept that Schmahmann proposed as the *"fundamental mechanism underlying disorders of intellect and emotion resulting from cerebellar dysfunction"* (23).

Neuropsychological deficits in patients with isolated cerebellar infarcts were reported by another fMRI study, where the brain blood-oxygen-level-dependent (BOLD) imaging was investigated during the n-back task (24). The study reported activity in the medial cerebellum and provided evidence for a cortico-cerebellar circuitry involved in WM tasks; cognitive impairments of patients with cerebellar lesions can be attributed to a disruption of afferent or efferent fibers of the circuitry. Increased BOLD response in angular gyri and the inferior parietal lobule was also recorded, which may be an expression of the compensation process evoked to counter the impairments due to a damaged cerebellum. These findings point to the cerebellum as part of a cortico-cerebellar network implicated in WM.

Even though a sizeable body of evidence, the neurobiology of WM remains in part unclear. Neuropsychological dissociations, dual-task experiments, and studies of patients with focal brain lesions are critical to understanding the functions executed by distinct brain areas, although researchers support the idea of distributed neural circuits and argue that trying to confine cognitive features would result simplistic. Moreover, many cognitive neuroscientists treat WM and sustained activity as equivalent, even if recent findings suggest the existence of cellular mechanisms that

could allow WM without sustained activation (25). Activity-silent mechanisms of latent WM could underlie the potential for WM without sustained activation in the hippocampus and other brain areas, which have been rejected from typical brain imaging studies.

1.2.3. Cerebro-cerebellar pathways

The cerebellum exerts its functions in close communication with the cerebral cortex through two main pathways: the efferent cerebello-thalamo-cortical (CTC) pathway and the afferent cortico-ponto-cerebellar (CPC) pathway (27).

The CPC pathway involves cerebral cortex neurons innervating pontine nuclei in the brainstem, which project as mossy fibers via the contralateral middle cerebellar peduncles to synapse on neurons of the internal granule cell layer and, finally, on dendrites of Purkinje cells (27). Purkinje cells in the cerebellar cortex project to subcortical structures imbedded in cerebellar white matter, the deep nuclei. The dentate nucleus is the most important among the deep cerebellar nuclei and receive most of its connections from the lateral hemispheres of the cerebellum. The axons of the dentate proceed, passing through the superior cerebellar peduncle, to the thalamus and then, via thalamo-cortical fibers, to multiple regions of the cerebral cortex (28,29) carrying out the CTC pathway.

These cerebro-cerebellar connections are thought to form closed-loops, with the feedforward and feedback branches passing mainly through CPC and CTC pathways, respectively (29). Thanks to these loops, the cerebellum is thought to operate as an information processing system that modulates cerebral activity (28). These loops might be closed either by direct connections of the same cerebral areas or pass through intra-cerebral connections both concerning sensorimotor and associative intermediate loops (29). Ide and Li provided evidence that through the connectivity with the thalamus and frontal regions, the cerebellum mediates error-related processing, hence it is possible that the cerebello-thalamo-cortical pathway is involved in executive function and error-related control (30). Traditionally, cerebro-cerebellar circuits were believed to function primarily in the domain of motor control, suggesting the output of cerebellar processing to be directed at a single cortical area, the primary motor cortex (M1) (31). After anatomical studies it is now clear that the site of termination of cerebellar efferents is not restricted to the subdivisions of the ventrolateral thalamus that innervates M1.

A 2017 study (29) mapped contralateral cerebro-cerebellar loops in humans *in vivo* through advanced tractography. Findings revealed proportions of CPC streamlines reaching different cerebellar and cerebral cortices: 8% of the CPC streamlines leaves the PFC and involves cerebellar lobules VIIb/VIII, while the parietal lobe encompasses 9% of the CPC pathway. Several studies in primates have indicated that cortico-pontine projections from frontal regions tend to be distributed along medial portions of the pontine nuclei, whereas parietal and temporal regions project to lateral pontine regions (32).

By investigating the extent organization of cerebellar input to different regions of the cerebral cortex, researcher stated that thalamo-cortical fibers reach mainly the prefrontal cortex and the temporal lobe (29). Cerebellum projects via the ventrolateral portion of the thalamus to the DLPFC (9, 46 BA), and projection to the PFC and M1 originate from different regions of the dentate nucleus (33). Thus, not only the DLPFC is targeted by cerebellar outputs, but these outputs appear to be topographically organized. By comparing the human to the macaque monkey CPC system, Ramnani and colleagues found a relatively large prefrontal contribution to the human CPC pathway in the cerebral peduncle (34). Desmond and colleagues (35) have suggested a model for neural substrate of verbal WM, based on cortico-cerebellar information processing and composed of two loops: a frontal- superior cerebellar articulatory control system, including the left inferior gyrus and the right superior cerebellar lobule VI/crusI; and a parietal- inferior cerebellar phonological storage system, including the left inferior parietal sulcus and the right inferior cerebellar lobule VIIb/VIIIa (36). Interestingly, inferior right hemispheric cerebellar activation in lobule VIIB, in contrast to the bilateral superior cerebellar activation, was observed only for the WM task and not during the articulatory control task, suggesting that superior and inferior cerebellar regions are sensitive to different cognitive requirements (36).

During WM tasks, increased activations is detectable in the cerebellar, frontal and parietal regions as well as in the pons and the thalamus (37). Increasing connectivity of the ponto- superior cerebellar tract was found to correlate with increased response time for a verbal WM task, implying that the structure of ponto-cerebellar projection contributes to individual differences in verbal WM. Moreover, increased activity in the inferior cerebellum seems to be associated with increased item recognition capacity (38) and the transient lesion to the superior cerebellum with increased response time during Sternberg memory task (39). These results provide support to the cerebellar role in cognitive functions, such as WM.

2. HEALTHY DEVELOPMENTAL TRAJECTORIES OF THE WORKING MEMORY NEURAL SUBSTRATE

The remarkable increase in working memory (WM) ability observed between 5 and 19 years of age is about 23 times greater than its decline during aging (40). As the infant becomes a child and the child approaches adulthood, more facts are learned, more problems can be solved, and more types of new learning become possible. Hence the difficulty to detect the actual causality of the development of cognitive processes. Studying the neural substrate of these fundamental processes of growth can indeed help us better comprehend how our mind works.

2.1. Cerebral development

Cortical gray matter volume grows and peaks at around age 10 to 12 in both prefrontal and parietal cortices. Synaptic pruning then occurs at different rates, within the PFC, gray matter reduction is completed earliest in the orbitofrontal cortex (OFC), followed by the VLPFC, and then by the dorsolateral prefrontal cortex (DLPFC). It has been argued that differences in maturational time course between prefrontal subregions partially account for differences in the rate of development of distinct cognitive control processes (41). Unlike gray matter, white matter volume increases with age, with myelination and increasing axon thickness. Diffusion tensor imaging (DTI) studies have demonstrated greater coherence of white matter tracts in adults than in children, as measured by an index of fractional anisotropy (FA). Greater coherence is associated with better performance on tasks that require interaction between regions that are connected by these tracts. In summary, both cortical pruning within brain regions and increased neuronal connectivity within and between regions could underlie improvements in cognitive control over development (41).

2.1.1. Infancy

Attention systems and recognition memory emerge from infancy studies as precursors of a much more complex ability, WM. The general attention system is functional in early infancy, although it develops considerably until early childhood with increasing sustained attention and decreasing distractibility (42).

In the newborn period, looking and visual fixation are believed to be primarily involuntary, under the control of the reflexive system involving the superior colliculus, lateral geniculate nucleus, and primary visual cortex (43). At around the third month of life, the posterior orienting system reaches functional onset, with the maturation of the posterior parietal cortex, frontal eye fields, and several subcortical structures such as the superior colliculus, pulvinar, and the locus coeruleus in the brainstem. The posterior orienting system enables voluntary control of eye movement, allowing controlled scanning of stimuli. As these areas develop, from 3 to 6 months of age, infants will show a greater ability to voluntarily engage, shift, and inhibit visual fixation (44). From 6 months on, as frontal areas (inferior and superior prefrontal cortex and anterior cingulate) mature, the anterior attention system becomes functional, and the infant capable of voluntarily maintain attention toward a central stimulus while inhibiting attention to distractors. This voluntary control of attention allows the child to actively maintain sustained attention and represents an early example of executive attention (44). Sustained attention is manifested as a significant and sustained decrease in heart rate from prestimulus levels that occurs when infants are actively engaged in an attentive state. Recording heart rate variability (HRV) allows researchers to measure focused attention development, which has been proven to have a direct influence on WM tasks (45, 41). Significant gains on WM tasks overlap in developmental timing with key periods for the development of sustained attention and the anterior attention system.

Much of the research on WM in infancy has focused on the A-not-B task and other delayed response (DR) tasks. In the standard version of this task, infants watch as a desirable object is hidden in one of two possible locations (A), after a brief delay is imposed, infants are allowed to reach the object. This trial is usually repeated several times before changing the hiding place. The A-not-B error occurs when participants continue to reach for the object in the original hiding location (A) after observing the reversal of the hiding place (B) (46). The perseverative error suggests a lack of *object permanence*, a concept introduced by Jean Piaget, that indicates the understanding that an object exists even if out of sight. Object permanence is a critical cognitive process that requires the ability to pay attention to an object and maintain visual memory and is considered an early stage of WM development.

The A-not-B error could be due to a lack of inhibitory control in younger participants and attributes higher success rates in older infants, around 8 months of age, to further maturation of DLPFC (42). Moreover, researchers have proven that response modality affects the results of the task, known as reaching-looking performance dissociation. In a 2010 study, infants performed higher object

permanence scale scores on the looking version of the task from 5 to 8 months of age, with an equivalent performance at 9 and 10 months of age (46). Overall infants performed better on looking reversal trials, while reach responses were less likely to be correct and more likely to be perseverative; this can be due to the fact the latter requires additional planning and cognitive sources (47). In a study conducted by Bell M. (48), higher performance of 8-months-old infants on the looking version of the A-not-B task was found to correlate with higher levels of frontal-parietal and frontal-occipital EEG coherence, as well as decreased heart rate from baseline to the task. Low-performance group of infants in this study could have less developed patterns of neuronal connections between frontal and parietal areas, consistent with adult studies of traumatic brain injuries (49). Taken together, these findings provide support for the role of a frontal-parietal network in WM tasks in infancy.

Gains in short-term capacity are linked to WM development. The capacity limit of stored information can be detected in infants using the change-preference task, where a longer visual fixation to the changing set of stimuli means novelty of the item presentation. Capacity seems to increase from 1 to 3 items across the second half of the first year of life (50, 51). A study found that 6 months old infants store rudimentary multiple object representations, while detailed representations are reached with maturation, this is because the focus of attention is limited to at most a few objects at once (52). This suggests that infants' WM supports an object representation that is featureless.

2.1.2. Childhood, adolescence, and adulthood

Since infants cannot carry out adult-like procedures, and older children cannot perform infant procedures without importing a host of strategies unavailable to them, there's a gap between infant- and child-based research in behavioral psychology and neuroscience. There are some fundamental differences between the anatomy underlying the developing and mature WM systems. Moreover, a recent study suggests that WM skills across the lifespan are driven by domain differences, such as verbal or visuo-spatial stimuli, rather than functional differences like maintenance and manipulation (40).

A study compared children from 4 to 11 years in multiple tasks, measuring 4 different memory components: verbal STM and WM and visuospatial STM and WM (53). A steady improvement in accuracy across age groups for each component was found, except for verbal STM which leveled

off sooner than the others. The main finding was that the basic modular structure of WM is placed by 4 years of age, and improves in capacity from childhood through to adolescence, while improvements of executive aspects of WM occur later in development. Event-related fMRI longitudinal studies have demonstrated increasing engagement of the superior frontal sulcus (SFS) and intraparietal sulcus (IPS) throughout childhood and adolescence in maintenance-related visuospatial working memory (VSWM) tasks. A positive correlation was also found between age-related increases in VSWM capacity and brain activity in the superior frontal and intraparietal cortex, in subjects between 9 and 18 years old (54). This may be since the parietal area is among the last brain regions to myelinate. Myelination of the parietal cortex increases transmission speed locally and between parietal and frontal cortices, resulting in a more stable and interference-resistant frontoparietal network.

The maintenance of online information involves the ability to suppress interference. During distractions, children exhibit greater SFS activation, while adults further engage the right DLPFC and bilateral intraparietal cortex (55), we deduce that children and adults rely on different regions to create a distractor-resistant memory trace. This suggests that developmental transitions in brain circuitry include both quantitative changes in the recruitment of necessary WM regions and qualitative changes in the specific regions recruited into the functional WM circuitry. Another example of qualitative changes is detectable in ventromedial regions, such as the caudate nucleus and anterior insula, which is primarily engaged during childhood, however, with the beginning of adolescence, VSWM ability begins to depend on the DLPFC, while the contribution of subcortical regions begins to fade (56). These findings are consistent with studies that report that ablation of DLPFC in adolescent monkeys causes severe WM deficits, while the same lesion in infant monkeys causes only minor impairments (57).

An fMRI study by Crone and colleagues (58) focused on the neural substrates that support developmental changes in the ability to maintain and manipulate information in WM. The regions of interest were DLPFC, the ventrolateral prefrontal cortex (VLPFC), and the superior parietal cortex. Maintenance trials were better performed by older participants, despite the similar recruitment of VLPFC across age groups. During manipulation trials, adults and adolescents recruited DLPFC and superior parietal cortex, while children failed the recruiting these regions during the delay period. Consistently with the fact that the ability to manipulate items in WM develops more slowly than the ability to simply keep items in mind. Interestingly, the study reported that children did recruit DLPFC and superior parietal cortex during encoding and response selection, just not during the delay

period, when manipulation was required. This implies a general point about developmental changes in brain functions: a region can exhibit adult-like patterns of activation in one task although not in another.

A longitudinal study used fMRI and diffusion tensor imaging (DTI) to analyze the dynamics of WM development during childhood and adolescence (6-25 years). In the cross-sectional analysis, current WM capacity correlated with activity in frontal and parietal regions, cortical thickness in the parietal cortex, and white matter of frontoparietal and frontostriatal tracts. In the longitudinal analysis, caudate activity and white matter structure correlated with WM capacity two years later, suggesting how white matter integrity, provides a basis for the development of future WM capacity (59).

2.2. Cerebellar development

The cerebellum is one of the first brain structures to start its differentiation, yet is one of the last to achieve its mature configuration, the cellular organization of the cerebellum continues indeed to change after birth (60, 61). Motor and cognitive development are equally protracted, fine motor control, bimanual coordination, and visuomotor skills are not fully developed until adolescence (62). Like the cerebral cortex, the morphogenesis of the cerebellar cortex is characterized by phases of neuronal proliferation, migration, differentiation, axon growth, synaptogenesis, and pruning. A longitudinal morphometric study found that, among that subjects, total cerebellum volume followed an inverted U-shaped developmental trajectory peaking at age 11.8 years in females and 15.6 years in males (63).

At 17 gestational weeks (17W), superior, middle, and inferior cerebellar peduncles pathways are already detectable, while connections between deep cerebellar nuclei and the cortex are not observed until 38W. A recent study examined cortico-ponto-cerebellar (CPC) and cerebello-thalamo-cortical (CTC) white matter tracts during early stages of brain development, between 29 and 44 weeks postmenstrual age. Findings indicate that the third trimester of pregnancy is a critical period for the development of the cerebellum, CPC, and CTC pathways. Hence, infants born preterm, before 37 weeks of gestation, may lack the maturity of white matter connections between the cerebrum and cerebellum (64). This evidence is consistent with a study by Takahashi and al., where is argued that cerebellar white matter tracts do not myelinate uniformly, but along a temporal

gradient starting from the archicerebellum, and finishing with the neocerebellum. Myelination starts during the third trimester and continues after birth; except for the middle cerebellar peduncle (MCP), which begins its myelination process some weeks later, around the time of birth (65).

Cerebellum seems to be not uniformly influenced by development and aging during adolescence and midlife, its volume follows distinct development trajectories depending on the zone. For example, the volumetric pattern of the posterior cerebellum seems to follow the protracted developmental pattern of the pre-frontal cortex, reaching maturity during adolescence (66). Relationships between size and function are complicated by the inverted U shape of developmental trajectories and by the many cytoarchitectural factors contributing to structure size. Furthermore, the functional specificity of different regions of the cerebellar cortex is conferred in large part by their membership within particular cerebro-cerebellar loops, because of its cytoarchitectural uniformity (63).

3. CEREBRO-CEREBELLAR FUNCTIONAL AND STRUCTURAL OUTCOMES FOLLOWING PERINATAL BRAIN LESIONS IN VERY PRETERM SUBJECTS

3.1. Preterm brain injury

Preterm delivery affects 10% to 11% of all births worldwide, with 1%-2% of all infants born very preterm (VPT <32 weeks of gestation) or at very low birth weight (<1500gr). Infants born VPT are vulnerable to brain injuries, which have the potential to disrupt subsequent neurodevelopment (67). Because of major advances in neonatal intensive care, nearly 90% of VPT infants now survive the neonatal period (68). During the latter, fiber organization and myelination of VPT infants may not keep up with that taking place in the brains of term-born children who are still in the intrauterine environment (69).

The most frequent type of brain damage in newborns is hypoxic-ischemic encephalopathy (HIE), which happens when the brain does not get enough oxygen or blood flow for a long period of time. Neonates exposed to hypoxic-ischaemic injuries, even at term, are at risk of myelin and axonal disruptions resulting in white matter abnormalities, which have been shown to correlate with impaired neurodevelopmental outcomes (68). Incomplete development of the vascular supply to the cerebral white matter and impairment in the regulation of cerebral blood flow to the periventricular area of the brain results in the most common brain injury among preterm infants: Periventricular Leukomalacia (PVL). The pathogenesis of PLV relates to diffuse vulnerability of the oligodendroglial (OL) precursor cells, which develop later into mature OLs and form the myelin of the cerebral white matter. Thus, the principal neuropathologic sequela of PVL is a reduction of white matter volume (70).

Intraventricular hemorrhage (IVH) is another major complication of prematurity and is primarily attributed to the intrinsic fragility of the germinal matrix vasculature and the disturbance in cerebral blood flow. When the hemorrhage is substantial, the ependyma breaks, and the cerebral ventricle fills up with blood (71). Bleeding in the brain leads to cell damage and brain injury.

3.2. Development of premature brain following PBI

Preterm birth and perinatal brain injury (PBI) are associated with altered brain development, due to abnormalities in axonal sprouting, dendritic proliferation, synaptic and intracortical myelination, and vascular elaboration (72). Prominent changes in brain morphology following PBI persist during childhood, adolescence, and adulthood.

Longitudinal assessments at 8 and 12 years old, reported both pruning and myelination to be weaker and delayed in preterm subjects when compared with term controls. Furthermore, significant correlations were reported between white matter integrity and both birth weight and gestational age (73). Nosarti and al. (72) investigated white and gray matter distribution in VPT adolescents demonstrating alterations in brain structure compared to term-born peers. Concerning gray matter, VPT subjects showed decreased volume in the bilateral temporal lobe including putamen, insula, and precentral gyrus; inferior frontal gyrus, cuneus, and precuneus; fusiform gyrus bilaterally, cerebellum, thalamus and right caudate nucleus. Lower white matter in VPT adolescents was diffused and observed in the brainstem, internal capsule, subthalamic nuclei, and pons, in temporal and frontal regions including the anterior cingulate gyrus, occipitofrontal fascicles, and cingulate cortex. A 2022 study investigated brain volumes of VPT-born adults, compared with their term-born siblings (74); the VPT group had smaller absolute brain volumes, less gray matter, larger ventricles, smaller thalami, caudate nuclei, right hippocampus, and left pallidum.

Reduced functional anisotropy (FA) of the corpus callosum, corticospinal tract, and superior longitudinal fasciculus were reported in VPT individuals compared to term-born control (75). The corpus callosum prolonged development is thought to be involved in the acquisition of adult-level cognitive skills during adolescence. The late spurt growth of the corpus callosum in the VPT adolescents (13% compared with only a 3% volume increase in controls) might represent a neuroplastic response of an under-connected brain attempting to improve the efficiency of its connections (76). Late neuroplasticity does not completely compensate for early white matter damage, since adults born VPT continue to underperform on neuropsychological tests compared with their term-born peers.

3.2.1. Disruption of WM neural network following PBI

Preterm born individuals have an increased risk for developmental problems in the motor, cognitive, and behavioral domains (77). Working memory (WM) is commonly affected in childhood and adolescence following VPT birth (77,68), MRI studies have highlighted functional alterations of the neuroanatomical substrates of memory during development. WM deficits in VPT correlate with surface area reductions in the orbitofrontal cortex, insula, parietal lobe, lateral temporal cortex (78), striatum, thalamus, posterior ventromedial prefrontal cortex, bilateral temporal pole, fornix, thalamus, parahippocampal cortex (79). Structures that show reduced activation in VPT adolescents compared with controls during WM tasks are bilateral DLPFC, lateral and medial posterior parietal cortex, left dorsomedial PFC, ventrolateral PFC, occipital lobe, anterior cingulate cortex, insula, lingual gyrus and cerebellum (80,75,81). VPT young adults with evidence of PBI displayed decreased brain activation in the inferior, middle, and superior frontal gyri (BA9) extending to the DLPFC, during an n-back task (82).

Allin et al. (67) found smaller cerebellar volumes in a cohort of adolescents born preterm compared with matched controls born at term, with a significant association between cerebellar volume and cognitive function. Early cognitive and motor development of preterm infants seems to be more strongly associated with white matter injuries than cerebellar volume (83), while 7-year volumes and growth of the cerebellum are more commonly associated with neurodevelopmental outcomes than TEA volumes (84). A 2016 study explored the association between diffusion measures of the cerebellar peduncles and IQ, motor, language, and WM outcomes, in a cohort of VPT children at 7 years of age. Significant correlations between diffusion parameters of the middle and superior cerebellar peduncle and neurodevelopmental outcomes were highlighted, suggesting a protracted effect of prematurity-related cognitive impairment on the brain at the microstructural level of the cerebellar pathways (85).

Structural alterations to the dorsal cingulum are common among VPT subjects with evidence of PBI, as this tract passes close by the lateral ventricles and lies superior to the corpus callosum, where neonatal hemorrhage often occurs. A 2015 study (80) investigated functional and structural brain discrepancies between adults with documented PBI, VPT adults without evidence of PBI, and term-born controls. The PBI group reported reduced volume and hindrance-modulated orientational anisotropy (HMOA) of the dorsal cingulum tract. PBI-related lower activation, during a WM task, was found bilaterally in dorsolateral PFC, posterior parietal cortex (lateral and medial), left dorsomedial and ventrolateral PFC when compared with the control group. Also reduced bilateral

cerebellar activation was found in the PBI group, suggesting strong functional connectivity with frontoparietal regions and its involvement in the WM network (80).

3.2.2. Crossed cerebro-cerebellar diaschisis following PBI

Cerebellar volume decreases by 3.11% during late adolescence in individuals born VPT, while remaining stable for term-born control peers (86). Cerebellar hypoplasia in the absence of direct cerebellar parenchymal injury is a prominent feature in preterm infants, especially those born very and extremely preterm (87, 88, 89). Recent studies highlight differential cerebellar maturational trajectories in VPT compared to full-term children, underling how brain injuries during a developmentally vulnerable period may lead to inadequate wiring and poor trophic interaction with the cerebellum, and ultimately underdevelopment (84, 90, 83).

Diaschisis represents the best example of remote network dysfunction in the human brain, which may be defined as the impairment of a brain region not directly affected by a pathological process (91). Crossed cerebro-cerebellar diaschisis consists in a matched reduction in metabolism and blood flow in the cerebellar hemisphere contralateral to the supratentorial lesions (92). Numerous studies support the association between cerebellar diaschisis and PBI in VPT subjects (92,93,94). As said before, cerebellar hypoplasia might occur secondary to cerebellar diaschisis and may be seen years after the damage (91), which is consistent with the evidence of reduced cerebellar volume reported in VPT adolescents. To date, cerebellar hypoplasia is one of the most common complications in preterm infants associated with poor neurodevelopmental outcomes (94, 95).

CONCLUSIONS

In this overview I analyzed the nature and role of altered cerebellar development in mediating adverse neurodevelopmental outcomes in very preterm subjects with documented perinatal brain injuries. I focused on evidence covering healthy and disrupted development of neural substrates, and related circuits, for working memory; along with working memory assessments outcomes discrepancies between healthy and VPT subjects.

VPT subjects with documented supratentorial injuries report cerebellar hypoplasia, caused by impaired cerebro-cerebellar connectivity: crossed cerebellar diaschisis. Since diaschisis implies the existence of an underling functional system within the engaged brain regions, I hypothesize that evidence of crossed cerebellar diaschisis and concomitant impaired WM outcomes converge to infer a functional role of cerebellum in WM.

This is just a starting point, we must further research, test, and eventually update, for the understanding of our brain, our functioning, and our humanity.

ITALIAN SUMMARY

Questa overview si propone di individuare evidenze a supporto del coinvolgimento cerebellare in funzioni cognitive, specialmente nella memoria di lavoro. Nel primo capitolo viene presentato il concetto di memoria di lavoro, in inglese, working memory, individuando i modelli teorici che nel tempo hanno più contribuito alla concettualizzazione di un working memory network. La disamina prosegue, da una prospettiva neuroscientifica, integrando i risultati provenienti da studi che, servendosi di diversi metodi di ricerca, si sono proposti di individuare le basi neurali del working memory network. Corteccia prefrontale, corteccia parietale e cervelletto sono risultate le regioni neurali di maggiore interesse per questa trattazione, è stato quindi di fondamentale importanza analizzarne le connessioni.

Capacità e abilità coinvolte nella memoria di lavoro si potenziano nel corso dello sviluppo, dall'infanzia sino alla prima età adulta, il secondo capitolo si propone di coglierne la causalità, indagando lo sviluppo sano delle regioni cerebrali e cerebellari individuate come basi neurali del working memory network. Il terzo capitolo affronta gli esiti funzionali e strutturali che coinvolgono il cervello e il cervelletto a seguito di lesioni perinatali in soggetti prematuri, le quali alterano i tratti di sostanza bianca cerebrale, fondamentale alla connettività dei diversi sistemi cognitivi, tra cui la memoria di lavoro. Le lesioni perinatali sono associate ad uno sviluppo cognitivo alterato e a cambiamenti persistenti nella morfologia cerebrale e cerebellare, tra questi vi è il fenomeno di diaschisi: una diminuzione del metabolismo neuronale e del flusso ematico cerebrale causata dalla disfunzione di una regione cerebrale strutturalmente separata ma funzionalmente correlata. Le lesioni perinatali in questione compromettono aree sopratentoriali implicate nel working memory network, e la relativa rete di connessioni frontoparietale.

Diversi studi riportano evidenze di ipoplasia cerebellare in adolescenti prematuri con lesioni perinatali posti in confronto a individui sani. È dunque consequenziale dedurre una causalità tra questi fenomeni, utile al sostegno dell'ipotesi di un coinvolgimento cerebellare nel working memory network.

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