Executive function and action: ontogenetic restraints

Ch. Njiokiktjien*

Abstract
It is generally acknowledged that there is no simple relationship between functional competence and any given dimension of neural development. We highlight some aspects of development in a clinical perspective and point to some models of brain functioning, in particular motor action programming and execution. The underlying neural systems of these functions will be discussed, notably the frontal brain. These systems develop slowly in normal children and may be at risk if there is poor development.

Functioning in daily life is praxis and speech or executive function in the broad sense. Therefore, one should always consider the possibility that deficiency of executive control functions in the narrow sense (impulse control, attention and working memory function) may be due to the slow maturion of the programming function of execution in the broad sense. One of the reasons for this slowness and the late coming into being of these functions in normal children is slow myelogenesis, a network component that determines optimal neuronal function. Moreover, slowly maturing pathway myelination is vulnerable to perinatal asphyxia and toxins. This especially affects the dorsal stream function, with a main final station in the premotor and dorsolateral prefrontal cortex.

Key words: ADHD – executive dysfunction – dorsal stream dysfunction – differential diagnosis

Introduction

Attention deficit disorders (ADD) are believed today to be for the most part so-called disorders of executive (control) function or EF, a term introduced by Luria [1]. The bulk of research points to abnormal attention regulation as well as problems with inhibition, while some of the children are also hyperactive (ADHD).

It is said that attention regulation in AD(H)D – sustaining stable attention, refraining from heeding irrelevant stimuli, keeping things in working memory and dividing attention between more than one locus, i.e. fluid disengagement and engagement – is abnormal.

On the question of children with AD(H)D, the present author would like to stress some ontogenetic tendencies that are connected to action, i.e. the development of praxis and speech. In particular he would like to call attention to how immature parts of the neural networks can inhibit young children before approximately the age of 10 from delivering an optimal performance compared to adolescents and adults. Today a number of neural network components are known to develop slowly and late, in particular myelination and synaptogenesis. Apart from these components, but not completely unrelated to them, certain neuronal nuclei are immature/abnormal as concerns their neurotransmitter production, specifically subserving behaviour as concerns 'attention for newness' (norepinephrine), anxiety/agression management (serotonine) and exploratory movement with efficient inhibition (dopamine). This will be not discussed here.

This article will discuss the following subjects: sensorimotor actions controlled by EF, brain areas playing a role in these actions, the ontogenetically slow developing areas and pathways that are limiting factors for action development, and the clinical consequences.

Which behaviours are controlled by executive functions?

EF is not a unitary concept; there are several levels. Levin et al. [2] reached consensus about the following EF in children: flexibility in problem solving, temporal organisation of behaviour, planning, inhibition and dividing and redividing attention. Later, Anderson [3] proposed four executive function domains: attentional control, cognitive flexibility, information processing and 'goal setting'.

Luria and Yudovich [4], using Pavlov's term 'autoregulation', connected in their and Vygotsky's view with behaviour under the influence first of social and thereafter inner speech, found that autoregulation is deficient in the case of frontal lesions. In the course of a child's development, according to Vygotsky, spoken language is integrated into practical thinking. Language plays a role in organizing higher psychological functions and in a sense penetrates the practical functions themselves [5]. Language has a mediating function in EF. For deficient autoregulation Barkley [6] recently introduced the term 'lacking rule governed behavior', e.g.in ADHD.

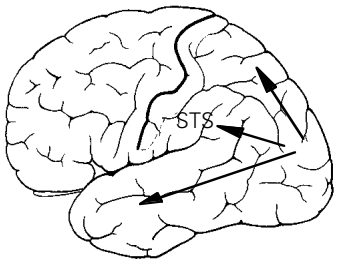
Int. symposium 'Children with ADHD: problems and solutions'. Arkhangelsk, Russia, May 19, 2005

EF does not exist on its own; it is a quality of an action. This action may be praxis (writing, handling objects and tools or one's own body in sports, etc.) or phasis (speech), but also 'passive' activities such as listening to speech or non-speech, watching and inspecting environmental scenes, watching a computer screen for a radar survey or for psychological tests.
Inner mental activities or 'thinking' and mental imaging, which consists of combined visual and auditory images and inner speech, are also controlled by attention function; obviously this is a working memory function without perception or visible action. Action develops more slowly than perception and the development of inner mental activity in ontogenesis is even slower.

Stuss [7] stated that there are three hierarchical levels of processing that interact: (1) sensory information/acquired knowledge; (2) EF in the narrow sense; (3) self reflection and metacognition.

The fact that a child knows that it has its own thoughts is a theory of mind function (although not quite equivalent to EF), for which frontal areas are necessary [8]. These levels also develop in this sequence and have an influence on final performance at a certain age. During infancy and early childhood and thereafter from 5 to 10 years of age, behavior changes dramatically as concerns attention, self reflection and expression. Motor persistence improves between 5 and 7 years of age and is a right hemisphere prefrontal function [9]. Motor impersistence is not rare and occurs in ADHD. Attentional control begins in infancy, while other EF functions mature between 7 and 9 years and are fully developed by 12-14 years of age [10]. Welsh et al. cited by Temple [11] proposed three frontally subserved maturation stages: simple planning and visual search processes are mature by the age of 6, a goal that has been set (the 'mental set') can be maintained and alternative hypotheses in the thinking process may be tested and there is also impulse control by 10 years of age; by 12 years there is adult verbal fluency.

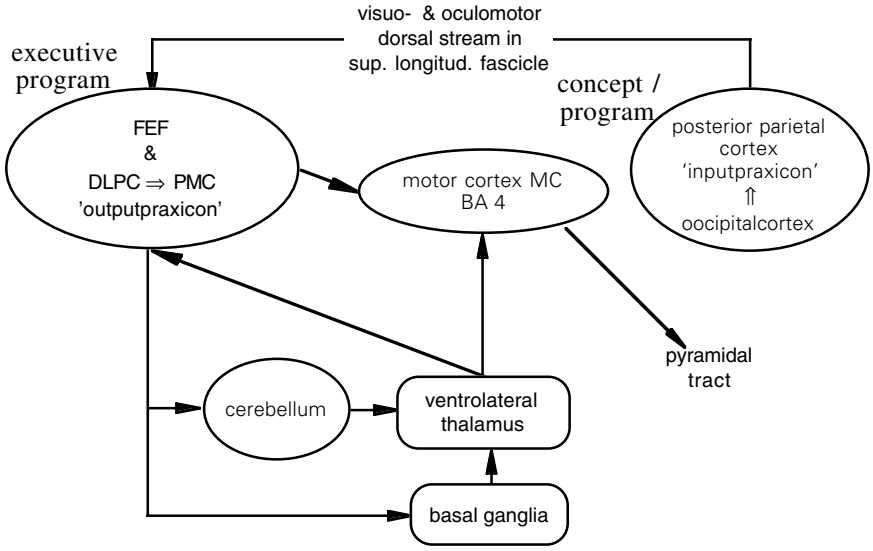
Figure 1 Pathways for visual perception and their integration in the programming and execution of motor acts



Dorsal & ventral visual pathways and their end points inferoparietal and ventrotemporal. A third pathway goes to the superior temporal sulcus (STS)

The dorsal stream (upper arrow) goes from occipital to posterior inferoparietal cortex (supramarginal gyrus BA 39 & BA 7b) and from there via the superior longitudinal fascicles to PMC and DLPC (lower picture). The parietal areas detect visual and kinesthetic form, spatial orientation and movement. They entail the 'inputpraxicon', mainly in the LH, and integrate visuokinesthetic afferent information into the existing procedural memory concepts for actions and make a new program for further actions. This program is transferred towards the left DLPC and PMC to execute movements for action (see Fig. 2b). The dorsal stream also conducts information from the posterior parietal area BA 7a towards both the FEFs to coordinate oculomotor action for fixing and following action, for example writing, catching and throwing a ball etc. One can also do these things with eyes closed, using the imaginary concepts from the left parietal areas and the SMA as well. Programming and execution are called ideomotor praxis and this, like spoken language, becomes an exclusive LH function at kindergarten age.

The ventral stream (lower arrow) goes from occipital to inferotemporal and from there to PMC and DLPC, not shown on the lower picture). This pathway identifies objects, faces, colours and whole words (gestaltperception more in the RH, details more in the LH).



The dorsal and ventral stream information (upper part of Fig. 1) are integrated in and transferred to the network for the motor program and executive control of it. Eye movements and FEF function, monitor all actions that require visual control.

The cortical motor program, described in Fig. 2b, is assisted by the basal ganglia and by the cerebellum for tone, balance, timing and attention functions.

The motor program is also controlled by the DLPC for working memory and flexible attention shifts.

There is also a continuous emotion and motivation flow from the limbic system towards the FL, not shown here.

For legends, see Fig. 2a and 2b.

Which brain areas play a role in action?

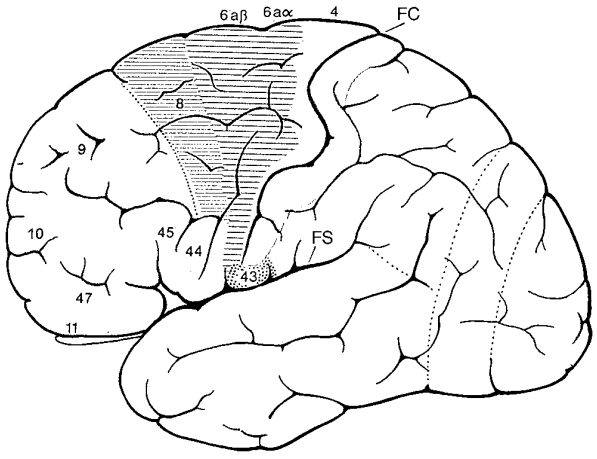
Visual perception areas in the occipital lobes divide into three pathways. There is a dorsal pathway for detection of location, spatial arrangement and movement and how to handle objects ('where and how' function), and a ventral pathway for identification of objects and faces (what and who function**)** [12,13]. A third pathway to the STS identifies facial, eye and body movements for social and emotion processing, possibly by mirror neurons, and the STS connects also ventral and dorsal stream functions. The dorsal and ventral information, different for the left hemisphere (LH) and right hemisphere (RH) [14], is transferred towards the frontal lobes (FL) for action. In this way the FL are perceptive; perception becomes action. Fig. 1 gives more details.

The frontal lobes (FL) have been called Luria's third functional block [Fig. 2a], the physiology of which has been inferred from disorders after damage to these lobes. Historically, the term 'frontal functions' was used; later on the term 'executive (control) functions' was introduced. However, the frontal lobes do not function as one functional system. Bradshaw [15] divided the frontal cortex into the following five areas, each with its own functional network: the motor cortex (MC), the oculomotor or frontal eye field (FEF), the dorsolateral prefrontal cortex (DLPC), the lateral orbitofrontal cortex (OFC) and the anterior gyrus-cinguli area [for a review as concerns development see Temple [11] and Bradshaw [15]; for a historical perspective see Benton in Levin et al.[16] and for executive functions Lyon and Krasnegor [17].

The FL are phylogenetic new areas and the ones which in humans are most evolved. Developmental behaviour changes are caused most obviously by the maturation of thes areas, histologically [18] as well as electrophysiologically [19]. Cell density is higher at birth than in adulthood. The areas are still difficult to separate and the absence of subcortical myelin is most noticeable [see next section]. The OFC matures earlier than the DLPC. Monoaminergic neurotransmitters, abundantly present in the FL, increase with age. For a review of the ontogenesis of the frontal lobes see Fuster [20]. There is also a prefronto-neocerebello-dendato-thalamocortical network. The neocerebellum (hemispheres) belongs with the prefrontal areas to the slowest developing structures in the brain.

The FL develop slowly and late and are therefore vulnerable for brain trauma and for asphyxia. They play a role in neurodegenerative diseases and developmental disorders such as developmental dysphasia, dyspraxia, ADHD, Gilles de la Tourette-syndrome (GTS), obsessive-compulsive disorder (OCD), autism and depression. In all these disorders there are problems with EF.

Figure 2a The frontal lobes and their cortical areas according to Brodmann (BA, Brodmann areas)



The frontal cortex occupies approximately 20% of the whole cortex and is subdivided in motor cortex (MC), premotor cortex (PMC), supplementary motor cortex (SMA) and prefrontal areas. The MC (BA 4) is darker gray. It contains the pyramid-shaped neurons that directly control the spinal cord, mainly for distal limb and oral movements. The PMC is marked by horizontal stripes and entails BA 6 for mainly complex proximal and axial motor control, BA 8 (the frontal eye field, FEF and BA 6αβ or SMA. The SMA subserves initiation of complex movements, bimanual coordination and imaginary motor function. Rostrally of the PMC are the prefrontal areas (shown in light gray) for EF.

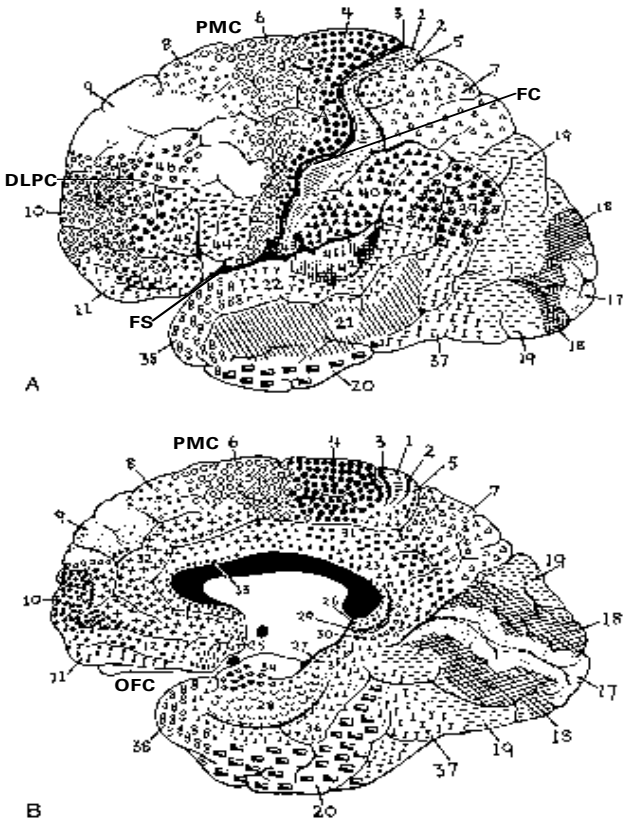
FC: fissura centralis (Rolandi)

FS: fissura Sylvii.
Pictures in Figure 2b gives additional details.

Here a global lateral view of the convexity of the brain is shown from the left side.

Slow development of this region has as a consequence that receptive functions and conceptual understanding, subserved by the posterior block, come into being earlier than expressive functions and action, i.e. speech and praxis and their executive control. Pathways connecting the posterior and the anterior brain, and pathways connecting both brain halves, undergo slow maturation as well.
The functional neuroanatomy of the FL is shown in Figures 2a and 2b.
The motor and premotor cortex. The dorsal PMC has a programming function for synergistic axial and proximal movements and has efferent connections with reticulospinal neurons. The ventral PMC (part of the Broca area) generates hand and finger movements and another part of the Broca area generates speech movements; both areas have efferent connections with the MC and make execution of these limb and speech movements possible [21]. Damage to the PMC only on the left and/or the right side results in contralateral clumsiness, slowness and loss of precision [22]. This is what Liepmann called melokinetic (or limb kinetic) dyspraxia. All these areas, the DLPC included, in the left hemisphere (LH) are called the outputpraxicon. The LH outputpraxicon is dominant for action and obtains already programmed commands from the inputpraxicon in the posterior parietal area in the LH; damage to the left inputpraxicon or its dorsal efferences leads to ideomotor apraxia on either side [23].

Figure 2b The frontal lobes and their cortical areas according to Brodmann (BA, Brodmann areas)



Legends (see also Fig. 2a): BA 4: motor cortex MC; BA 8: eye fields, together with BA 6 called premotor cortex (PMC); BA 44/45: Broca area; DLPC: dorsolateral prefrontal cortex (BA 9/46); OFC: orbitofrontal cortex (BA 11/13/14);

The main networks are the MC, the PMC, the SMA, the DLPC, the OFC and the anterior cingulum, not shown here.

The PMC projects on reticulospinal neurons and on the the MC for spinal motor neuron innervation. The PMC receives input from the SMA and DLPC. Part of the PMC is the so-called 'outputpraxicon', the endpoint of the dorsal and ventral visual perception stream and indirectly part of the visual system via the dorsal and ventral longitudinal fascicles [Fig. 5]. The outputpraxicon has control over 'how', 'where' and 'what'/wherefore stimuli are processed in the posterior parietal inputpraxicon and the ventral temporal areas. BA 8 is the FEF and BA 46 is the neighbouring eye field for spatial processing.

Analogous to input- and outputpraxicon there is the inputlexicon (Werrnicke) and the outputlexicon (prefrontal Broca areas BA 44 and 45).

The DLPC, the OFC and the anterior cingulum are involved in a network with projections on the basal ganglia. These ganglia project back on the frontal cortices via the thalamus (Fig. 1). Furthermore there are connections with the limbic system, the cerebellum and the brain stem. The OFC has social and emotional functions and processes the significance of stimuli for behaviour, for example rewarding stimuli like drugs and food. The dorsomedial prefrontal cortex (DMPC) is not shown here. This area has strong connections with the medial temporal areas.

The ascending connections to the frontal areas are serotonergic from the raphe nuclei of the brain stem, dopaminergic from the substantia nigra and the ventral mesencephalic tegmentum and noradrenergic from the locus coeruleus. Their dysfunction plays a role in the pathogenesis of ADHD.

Source: K.Brodmann: Vergleichende Lokalisationslehre der Grosshirnrinde, Leipzig 1909

The FEF, part of the PMC and also a projection field for the dorsal stream, has descending connections to the pons for eye movements. This area is important for looking at objects in the right direction during actions and for fixing on and following the objects as long as necessary.
A bilateral interruption of the pathways to the FEF causes Bálints optic ataxia. This syndrome also occurs, however, in children, more often than is noticed in a slight or covered form. Eye movements may also be directed by verbal command or by inner speech. Some children with reading problems cannot adequately fix or efficiently follow a word, a text or a moving object with saccadic movements; some children with AD(H)D have problems with oculomotor searching as well.

The SMA (medial PMC) can generate the same movements as the PMC without external stimuli, just by mental imaging. The SMA is also active in the initiation selection and the direction of motor sequences and for bimanual movements. Given clinical experience, one may suppose frequently SMA dysfunction in children.

The dorsolateral prefrontal cortex. The DPLC controls the preparation of movement combinations in the PMC, the executive process is responsible for the right place and time of movement combinations. During actions the DPLC mediates temporal contingencies in order to connect what has happened already and what will follow; this is a working memory function that entails sustained attention and flexibility as well as timing and duration sense. The working memory also has a role in the ontogenetic process of autoregulation (inner speech) and response inhibition in 'thinking behaviour' and 'doing'.

Attention deficit hyperactivity disorder. Alertness and sustained attention for simple tasks have a strong connection to a frontoparietal network in the RH. ADHD is partially based on a fronto-striatal function disorder [24]. ADHD is strongly connected to the right DLPC [25]. The clinical framework suggests an important role for the RH [26]. Morphometric studies show asymmetric abnormalities in the FL, the basal ganglia, the corpus callosum and the cerebellum.

Which are the ontogenetically slow developing areas and pathways that are limiting factors for behavioural development?

An important developmental process in cerebral axons, the fiber parts of neurons, concerns their myelination, promoting electrical isolation and quicker impulse conduction. Myelogenesis is a complicated biochemical and genetic process, controlled by food, as well as hormones and axonal activity [27].

Myelination studies were classically done post-mortem and microscopically; they can now, however, be done in vivo with increasingly sophisticated MRI techniques; one new tool is diffusion-tensor imaging.

Mylination begins in the 5th prenatal month and finishes at the end of the 2nd year, studied with conventional T_1- and T_2-weighted MRI. New MRI techniques show more subtle myelination changes.

Classically, researchers saw myelination progressing further, until approximately 10 years of age and later, notably in slowly maturing pathways, that subserve cognitive and executive functions [28].
It was shown that white matter increases from birth until adolescence – the central white matter earlier than the lobar – and that the increase of myelin contributes most to this increase in volume. The fact that connections obtain a more mature function has also been shown using electrophysiological methods, for example EEG coherence of callocal connections [29].

Myelination is not equally distributed in the brain. The beginning as well as the duration of the myelogenetic cyclus vary significantly in different parts of the brain and the sequence in which areas and tracts myelininate is also different [27]. Some pathways myelinate quickly and prenatally, some postnatally [30;28]; it takes sometimes years before full maturation is reached. In young prematures the brainstem, the vermis, parts of the thalamus, the basal ganglia and the hippocampus already partially contain myelin [31]. Long and phylogenetically new association fibers myelinate slowly and mature at a late age [Fig. 3 and Table I]. They connect according to the rule of Flechsig from the posterior to the anterior brain in the secondary and tertiary cortical fields. There is also developmental hemispheric asymmetry. For example with MRI, Paus et al. [32] showed that between 4 and 17 years the white matter maturation of the frontotemporal fasciculus arcuatus – between the Wernicke and the Broca area – occurs first in the left hemisphere. We restrict ourselves here to slowly maturing fibers. Myelination of these fibers goes in the direction of the stream of information. Systems which are active earlier myelinate first, and the areas innervated by these systems myelinate afterwards.

Figure 3 The most important long intra- and interhemispheric pathways in a sagittal (a), a transverse and frontal plane (b)

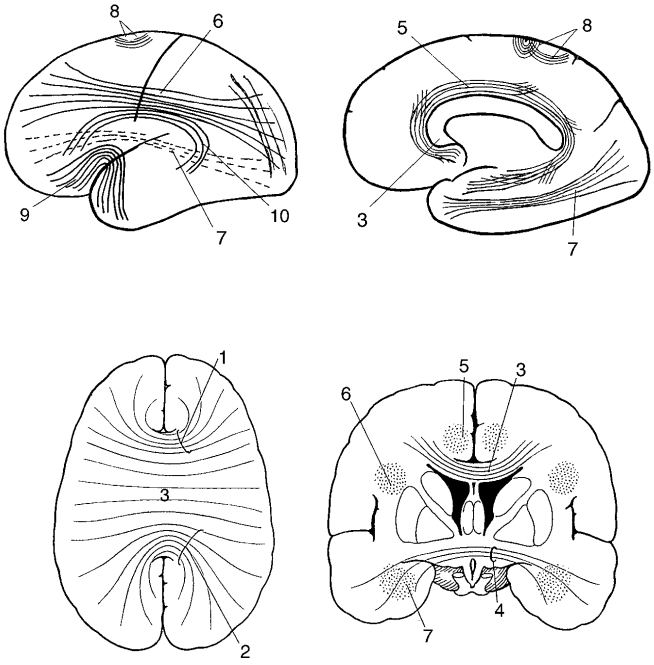


Figure 3a: On the left, the subcortical pathways are drawn, connecting mainly the secondary cortices. On the right, pathways are shown, located deeper in the subcortex. Fasciculus uncinatus (9); fasciculus arcuatus (10) connects the Wernicke and Broca areas. Other legends below.

Figure 3b: Commissural fibers, notably corpus callosum (CC) is shown in a transversal (left) and a frontal plane (right). On the left, forceps minor (1), forceps major (2) and other CC fibers (3); these fibers connect homologous secondary cortices in the left and right hemisphere.
On the right, there is a left-right view of CC fibers (3). The posterior commissure is invisible here, the anterior commissure is shown (4); cingulum (5). Longitudi-nal superior (6) and inferior fasciculi (7) are dorsal and ventral stream connections respectively; they are seen on the right in Fig.3b anterior-posteriorly and in Fig 4a in a sagittal plane. Arcuate fibres (8); uncinate fibres (9); temporofrontal and arcuate fascicles (10).

In Fig. 1 and 2 the dorsal and ventral pathways for perception and action are described as are the cortical areas for actions and their executive control.

The main intrahemispheric pathways are the superior and inferior longitudinal bundles, main parts of the dorsal and ventral perception stream respectively, the fasciculus arcuatus between the speech areas, the fasciculus uncinatus between the fronto-orbital gyri and the anterior temporal areas; a more deeply located part of this bundle connects frontal with occipital areas. Finally there is the medially situated cingulum that connects frontal and parietal areas with parahippocampal and temporal areas.

Table I Microscopic observation of pathways with late beginning and slow myelogenesis (MRI data)

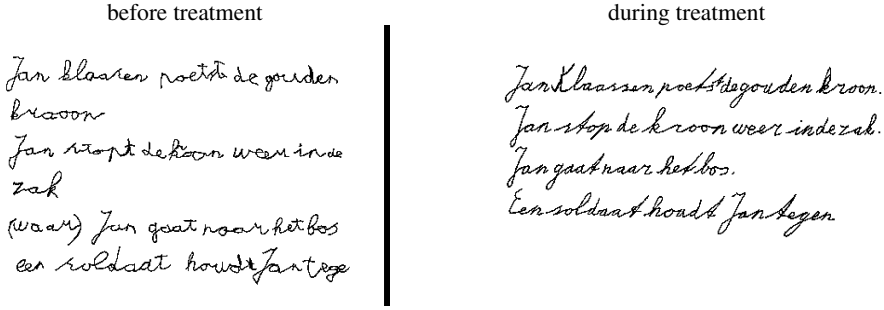
Pathway systems	Beginning of myelination	Maximum postnatally
commissura anterior	46 weeks	after years
corpus callosum	46 w (64 w)	5-9 years (10 months)
tractus mamillothalamicus	48 w	unknown
fornix	39 w	unknown
prethalamic exteroceptive and proprioceptive pathways. . .	20 w	1 year
postthalamic exteroceptive and proprioceptive pathways. . .	40 w (41 w)	1 year
capsula interna, anterior part	38 w (68 w)	after years (9 months)
pyramidal tract, e.g..corticobulbar tract	40 w	1 year
visual prethalamic tract	37 w	4-5 m
visual postthalamic tract	40 w (48 w)	5 years (4 years)
acustic prethalamic pathways	20 w	5 years
acustic thalamocortical tract	40 w	4-5 years
fibers from primary to secondary acoustic cortex.	40 w	3 years
fibers from secondary to tertiary acoustic cortex	40 w	3.5 years
intracortical neuropil in primary acoustic cortex	46 w	4 year
intracortical neuropil in secondary acoustic cortex	52 w	5 year
visual thalamocortical pathway.	40 w	56 m
intracortical association bundles, fasciculus arcuatus	40 w	7 years (0.5-1 year)
subcortical white matter, occipito-frontal	36-52 w	60 weeks

Table I shows the estimated starting times with the lowest degree of myelination and the estimated maxima in weeks gestational age, when there is no longer an increase in myelination. The length of the myelogenetic cyclus can be calculated with these data. The given data are based on the median statistic: at least 50% of the brains under study show a beginning or a maximum of myelination; maximum myelination means the standard myelination of a 28-year old adult [ref. 28 & 30]. Data obtained with conventional MRI are shown in parentheses [27]. These data show beginning myelination at a later age and the maxima are reached earlier, compared with the neuropathologic studies, a shift that is caused by methodology (less resolution strength of MRI).

Clinical consequences

If one examines children clinically or if one tests them in the neuropsychological laboratory, one will be confronted with deviant performance. A differential diagnosis has then to be made. The present author wishes to draw attention to the fact that performance may be less efficient because of abnormal EF. Alternatively motor actions may lack precision because of either inefficient visuomotor monitoring and/or inefficient visuospatial encoding in the inputpraxicon with subsequent poor programming towards the outputpraxicon. There may be disconnections along the entire trajectory of the dorsal stream. The cerebellar loop may also function in an immature way. An example is given in Fig. 4.

Figure 4. Handwriting before and during treatment of ADHD with methylphenidate



An objective criterion of the effectiveness of treatment in children with methylphenidate is often the improved quality of their handwriting, especially if that is poor before treatment [33]. This shows that handmotor precision improves through the change of neurotransmitter action at the endpoint of the visuospatial and coordinative visuomotor dorsal stream information in the frontal lobe. The example on the left could also be the handwriting of a younger immature child or an older child with a graphomotor dyspraxia after dorsal stream damage, but that would not have been changed with methylphenidate.

Conclusions

One should always consider the possibility that deficiency of executive control functions in the narrow sense (impulse control, attention and working memory function) may be due to slow maturation in the programming function of execution in the broad sense (action, i.e. speech and praxis). One of the reasons for this slowness and the late coming into being of these functions in normal children is slow myelogenesis, a network component that determines optimal neuronal function. Moreover, slow maturing pathway myelination is vulnerable to perinatal asphyxia and toxins. This affects especially dorsal stream function, with a main final station in the PMC and DLPC.

Author's professional positions and address

Dr. C. Njiokiktjien MD, PhD, neuropsychiatrist and child neurologist, member of the staff at the Developmental Dysphasia Foundation, Amsterdam.
Address: Honthorststraat 4, NL-1071 DD Amsterdam, The Netherlands; cn@suyi.nl.

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