University of Pisa

PhD Course in Basic and Developmental Neuroscience

Neuropsychological profile in children with neurodevelopmental disorders: new clinical and instrumental approaches to natural history and brain reorganization in cerebral palsy

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To all the children who allowed developmental neuroscience to advance, discover and help others

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Rationale and brief summary of the thesis

Neurodevelopmental disabilities are a group of disorders with onset in the developmental period characterized by alterations of the central nervous system due to early brain damage, genetic/chromosomal abnormalities, epilepsy or environmental conditions which can give rise to intellectual disability, neuropsychological deficits, specific learning deficits, movement and posture disorders, such as Cerebral Palsy, and psychiatric disturbances. Other neurodevelopmental disorders frequently co-occur and determine impairments in personal, social, academic, and vocational functioning (Diagnostic and Statistical Manual of Mental disorders, Fifth edition, 2013).

Neurodevelopmental disabilities are currently being studied based on different levels of description-behavioral, cognitive, neural-within a cognitive neuroscience framework, far distant from the adult domain-specific modularization approach. The modern cognitive neuroscience framework (Marechal et al., 2007; Johnson and de Haan, 2011) fuelled by recent breakthroughs in the fields of brain connectivity and genetics, posits that brain-behaviour relationships in childhood are best understood as being subsumed by progressive specialization and localization of function within the complex two-way interaction between genes and various environments.

Traditionally, neurodevelopmental disorders have been often investigated through the lens of single levels of description rarely correlating, in the same patient, neuropsychological, neurofunctional and psychiatric evidence.

The aim of this PhD thesis is to study Cerebral Palsy as a model of neurodevelopmental disability by integrating different levels of description for understanding such a complex and multifaceted neurodevelopmental disorder. According to the modern classification, Cerebral Palsy is described as "a group of permanent disorders of movement and posture causing activity limitation that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, perception, cognition, communication and behaviour, by epilepsy and by secondary musculoskeletal problems" (Rosenbaum et al., 2007). Current literature is underlining the crucial role of such associated deficits in determining outcome both in terms of neuropsychological and academic functioning as well as on a social, emotional and participation levels, and thus the limits of plasticity in the face of early damage to the central nervous system.

Five studies have been conducted to investigate, in children with cerebral palsy with bilateral white matter lesions, the neuropsychological profile and neuroanatomical correlates, the impact of the neuropsychological profile on psychopathological and academic problems, and the effect of an intensive cognitive training on neuropsychological functioning and on the neurofunctional mechanisms underlying plasticity. The aims were pursued by means of new clinical

and instrumental approaches: on a behavioural level of description, the Developmental Neuropsychological Battery-NEPSY-II (Korkman M, Kirk U, Kemp SL, 2007; Italian standardization Urgesi C, Campanella F, Fabbro F, 2011), a comprehensive neuropsychological investigation, and CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden), an evidence-based computerized program; on a neurofunctional level of description, a novel semi-quantitative scale for classification of brain MRI lesion severity (Fiori et al., 2014) and high density sleep EEG to measure changes in slow waves activity (electroencephalographic power between 0.5-4.5 Hz), crucial for regulating synaptic plasticity and cortical reorganization (Huber et al., 2004). Finally on a psychiatric level of description, psychopathological symptoms were investigated with a parent-report measure (CBCL, Achenbach et al., 1991).

In the first study the aim was to analyze the profile of neuropsychological strengths and weaknesses, by NEPSY-II, and their relationship with neuroanatomical findings on brain MRI in children with bilateral cerebral palsy due to periventricular leukomalacia and normal verbal intelligence (Study 1). The results showed a neuropsychological impairment profile characterized by a multi-level structure: visuo-spatial and sensorimotor skills were severely impaired in almost all of the children, while difficulties in attention and executive functions were an additional weakness specifically associated with the involvement to anterior/medial corpus callosum and thalamus. Language and verbal memory were confirmed to be a specific strengths in this clinical population.

The second study focused on the academic abilities in children with bilateral cerebral palsy to verify if there was a pattern of learning deficits specifically characterizing bilateral white matter lesions and not unilateral lesions. For this purpose, children with bilateral lesions were compared to age and intelligence matched children with unilateral lesions (Study 2). A high percentage (55%) of children with cerebral palsy showed reading or text comprehension difficulties and no significant differences across clinical forms of cerebral palsy were found, suggesting the different neurofunctional alterations leading to unilateral or bilateral brain lesion do not differently impact the compensative strategies for reading and text comprehension.

The impact of the neuropsychological profile on paychopthological problems was investigated studying the behavioural and emotional characteristics and their correlations with the clinical and neuropsychological profiles (Study 3). The findings showed that the internalizing problems, that is social withdrawal and somatic problems, characterized a high percentage of children (35%) and resulted strongly correlated with the degree of impairment in non-verbal intelligence level, visuo-spatial and manual motor abilities as well as social competences.

In the last year of the PhD project, an evidence-based training program has been administered to a sample of children with bilateral cerebral palsy due to periventricular

leukomalacia in order to improve the neuropsychological impairments, attention and executive functions, found impaired in Study 1 (Study 4). A significant, directly trained effect on working memory abilities was found independently of clinical characteristics. An additional not-directly trained effect on impaired neuropsychological functions, such as visuo-spatial, inhibition and verbal updating, was found to be correlated to the degree of impairment in gross-motor function and verbal intelligence level.

In a subgroup of children with bilateral cerebral palsy due to periventricular leukomalacia, the slow waves activity results at high density sleep EEG before and after training, have suggested new hypotheses on the neurofunctional mechanisms underlying plasticity such as sustained compensation or functional restitution (Study 5). Positive correlations between the improvement of impaired neuropsychological functions, such as visuo-spatial memory and manual planning, and the frequency-specific increase of the slow waves activities in fronto-occipital regions were found, suggesting a cortical reorganization process functionally connected with the trained neuropsychological domains.

The introduction of this PhD thesis is oriented to briefly describe the neurodevelopmental disorder, cerebral palsy, and to illustrate the new instrumental and rehabilitative approaches used to study this clinical disorder.

INTRODUCTION

INTRODUCTION

Cerebral Palsy: a brief introduction

Cerebral palsy (CP) is a well-recognized neurodevelopmental condition beginning in early childhood and persisting through the lifespan. The large amount of criticism and the different proposals that were submitted over the years to the definition of CP reflected and still reflect today, the uncertainly about the actual pathological features of the disease, due to symptom heterogeneity and to doubts related to its pathogenesis (Ferrari and Cioni, 2010).

To solve these issues, an international multidisciplinary team in 2004 proposed a new definition of CP, that has been revised in 2006 by the Executive Committee of the team: "*Cerebral palsy describe a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder"* (Rosenbaum et al., 2007). This definition underlines the idea that a comprehensive approach to Cerebral Palsy needs to be multidimensional and that management of patients with CP almost always requires a multidisciplinary setting. CP indeed is one of a group of neurodevelopmental disorders which involve numerous developing functions. Moreover as in other neurodevelopmental disorders, various manifestations of disordered brain function may vary in different individuals or at different periods, e.g. some aspects of the motor impairment, intellectual disability, epilepsy, attention difficulties, and many others may be more prominent, or more problematic, at different stages of the life of a person with CP (Ferrari and Cioni, 2010).

In CP, classification guidelines have always been drawn up according to the various movement disorders, namely, the different postural behaviours related to tone and the gesture performance characteristics (hypotonic, spastic, ataxic, choreic, atheoid, etc.), associated with their topographic distribution (tetraplegia, diplegia, hemiplegia, etc.). Therefore, the problem of CP classification is still pending. This complex disorder indeed cannot be exhaustively analyzed from just one explorative dimension, like motor assessment and its topographic localization.

To solve these issues, Ferrari and Cioni in 2010 proposed other clinical dimensions to classify CP: motor, perception and intentional perspectives. To evaluate palsy from the motion point of view (posture and gesture) the authors proposed to analyse the patient's movement repertoire (modules, praxias and action level) and his/her ability to use it (formulas and strategies). Regarding perception defects, they described three different levels of analysis, going from the periphery towards the center. The first level includes sensation, the capacity to collect basic

information (sensations) thanks to *"peripheral receptors which provide information (output) on the nature and degree of incoming stimuli (input), translating signal of completely different natures into a homogeneous language (action potential)".* The second level includes perception, the ability *"to compare, integrate and interpret sensitive and sensory information collected at the first level, trying to recognize any intrinsic coherence"*. The third level, representation, *"comprises central representation, or mental images, namely, maps representing the final destination for information, after being collected and processed through experience*". The re-description of representations is a process through which information, implicit in the mind, becomes explicit for the mind, initially relates to a particular domain and then extends to other domains (Karmiloff-Smith, 1992). The classification based on these three levels of functioning allows to evaluate the disorder from different point of views and to achieve useful information for diagnostic and rehabilitation assessment.

The most popular criterion for classifying CP has always been based on the topographic distribution of the motor impairment: tetraplegia, diplegia and hemiplegia. Taxonomically, no importance is given to the location and extension of the brain lesion, to the timing of the central nervous system damage (pre-, peri-, post-natal), to the etiology (prematurity, intracranical haemorrhage, cortical dysplasia, etc.) and pathogenesis (traumatic, toxic, infective), to neurological deficits associated with palsy (epilepsy, intellectual disability, sensorial, perceptive disorders, learning disabilities, etc.) and to other associated symptoms (Ferrari and Cioni, 2010). For these reasons, the criterion of topographic distribution of impaired movement, although generally accepted, is not exempt from criticism.

Cerebral Palsy, by definition, is caused by an early non-progressive brain lesion, the nature and scope of which are wide-ranging. Only the most common will be described below. Bilateral spastic CP (di- and tetraplegia) is first and foremost associated with periventricular leukomalacia (PVL), with or without additional lesions, in particular in children born preterm (Bodensteiner et al., 2006; Hoon, 2005; Krageloh-Mann et al., 2002; Okumura et al., 1997). Periventricular leukomalacia is a condition involving dilation of the ventricles and reduction of the white matter. The interruption of the motor tracts is the cause of movement deficits in children with bilateral spastic CP, but it has been hypothesized that white matter tracts connecting prefrontal and posterior brain regions, the basal ganglia, and related dopaminergic pathways may be compromised also, and thus will affect other functions of the brain (Christ et al., 2003).

A substantial part of hemiplegic CP may also be caused by PVL, but the reported frequencies of PVL differ among studies (Cioni et al., 1999; Krägeloh-Mann & Horber, 2007). Both unilateral and bilateral lesions are seen in children with hemiplegia (Okumura et al., 1007; Cioni et al., 1999). Other types of lesions seen in children with hemiplegic CP are brain malformations and

cortical/subcortical lesions due to infarcts, mostly in the region of the middle cerebral artery (Cioni et al.1999; Krageloh-Mann & Horber, 2007; Nelson, 2002; Okumura et al., 1997; Yin, Reddihough, Ditchfield, & Collins, 2000).

Children's development of cognitive functions requires a sufficient neural foundation. Low gestational age, low birth weight, and low fetal growth are considered risk factors for cognitive outcome in cerebral palsy (Hutton et al., 1997). The degree of neurological involvement is in fact a good predictor of the general level of cognitive functioning (Goodman & Yude, 1996; Krageloh-Mann et al., 2002). Particular patterns of lesions have mainly been correlated with cognitive functioning at a general level (e.g. Cioni et al., 1999; Krageloh-Mann et al., 1995; Krageloh-Mann et al., 2002; Serdaroglu et al., 2004). The cerebral lesions associated with CP represent a biological constraint that affects the typical developmental trajectory of different cognitive functions and often entails intellectual disability or specific cognitive impairments. Due to the nature of the underlying lesions, children with spastic CP can be expected to develop a wide array of cognitive impairments. A more specific examination of the cognitive impairments in different forms of spastic CP is discussed further below.

New instrumental approaches to study the neuropsychological profile: NEPSY-II, a developmental neuropsychological assessment

Theoretical framework

The NEPSY-II (Korkman et al., 2007) is a comprehensive, co-normed, and multidomain neuropsychological battery designed to assess neurocognitive abilities in children ages 3-16 years, based on Luria's theory. Alexander R. Luria (1902-1977), a Soviet neuropsychologist, was oriented at identifying brain structures involved in different neuropsychological functions such as attention, memory, language and visuo-spatial processes. In his theory, every high-level cognitive process investigated could be decomposed into several subcomponents in turn mediated by flexible, interactive neural networks. Therefore each complex function, such as language, memory, attention, motor performance and thinking, included several different subcomponents. Language functions included, for example, oromotor sequences, naming, short-term memory, linguistic elaboration, auditory phonological analysis. Luria's neurobiological view described the brain as a functional mosaic, considering each part responsible for different subcomponents. Furthermore, the same brain regions were also involved in different functions. Indeed, Luria hypothesized that at time one specific deficits (e.g. poor short-term memory) could affect many other complex functions, such as language comprehension, reading or writing, while other times the secondary effects could be more restricted (Luria 1980). Luria's theory also mentioned the maturation of the complex cognitive processes during the development, changing from the child's effortful execution of every subcomponents to the adult's automated execution. For example, a child automatically attends to a novel and interesting stimuli and acts impulsively, and the verbal rules, in conflict with direct impulses, little influence his behaviour. The ability to control attention develops in the child's interaction with the adult, firstly it is the adult that controls the child's behaviour with gestures or words, then gradually the child, internalizing these rules and verbal commands, is able to inhibit his behaviour and to control his attention.

Modern child neuropsychology recognized the complexity of cognitive functions, considering many types of subprocesses involved for each. Luria's theory provided the starting point in the development of NEPSY-II, nevertheless his principles were modified and integrated with contemporary models of child neuropsychology and with psychometric conventions.

History and development

The first version of the NEPSY-II, called NEPS, was published in 1980 (Korkman, 1980) in Finland. It originally consisted of only two to five tasks for 5- and 6-years olds, scored in a simple pass-fail manner, so that items were passed by the vast majority of children. The NEPS was revised and expanded in 1988 in Finland (NEPS-U, Korkman, 1988) and in 1990 in Switzerland (NEPSY, Korkman, 1990) including more tasks and expanding the age range (from age 4;0 to 7;11 years). The American version of the NEPSY was published only in 1998 (NEPSY, Korkman, 1998) and was composed of 27 subtests for children ages 3 to 12, assessing five domains: Attention/Executive Functions, Language, Sensorimotor, Visuo-spatial, and Memory and Learning. The North American version of the NEPSY was revised and expanded into NEPSY-II in 2007 (Korkman, 2007).

The authors indicated four primary goals for revising the NEPSY into the NEPSY-II (Brooks, 2010). Firstly, it was necessary to improve and expand the cognitive domains covered across the age span, extending the age range from 12 to 16 years and adding, removing or modifying the subtests. Several subtests were removed because of low clinician sensitivity, while new subtests were added in the new domain of Social Perception. Most NEPSY-II subtests were also modified in terms of administration, recording or scoring procedures, adding new items, and/or changing the age range. Secondly, the authors enhanced clinical and diagnostic utility of the NEPSY-II by removing the five domains scores in favour of the more clinically sensitive subtests-scores such as primary scores, process scores, contrast scores and behavioural observations. The third goal of the revision involved improving the psychometric proprieties of the NEPSY-II, such as concurrent validity, correlating it with various measures of academic achievement, intelligence and adaptive functioning. New normative data for each subtest were obtained also to improve floor and ceiling effects present in some NEPSY subtests. The fourth goal of the revision was to enhance the usability and ease of administration of the NEPSY-II subtests making it more flexible in terms of the possibility of choosing different subtests based on clinical assessment.

Currently, the NEPSY-II has been translated and standardized in Finnish (Korkman et al., 2008), in Dutch (Zijlstra et al., 2010), in Swedish (Korkman et al., 2011) and in Italian (Urgesi, Campanella and Fabbro, 2011).

Structure and purpose of NEPSY-II (Italian version)

The Italian version of the NEPSY-II consists of 33 subtests divided into six content domains: Attention and Executive Functioning, Language, Memory and Learning, Social Perception, Sensorimotor, and Visuo-spatial Processing (Table 1).

Table 1: NEPSY-II structure

Attention and Executive Functioning			
A1	Visual Attention	A4	Inhibition
A2	Design Fluency	A5	Clocks
A3	Auditory Attention	A6	Animal Sorting
A3	Response Set		
Language			
L1	Comprehension of instructions	L5	Semantic Verbal fluency
L3	Rapid Naming-response time	L5	Phonological Verbal Fluency
L3	Rapid Naming-accuracy	L6	Repetition of nonsense words
L4	Phonological processing	L7	Oromotor Sequences
Memory and Learning			
M1	Memory for faces	M5	Memory for names
M2	Word List Interference	M6	Narrative Memory
M3	Memory for design	M7	Sentence Repetitions
M4	List Memory		
Sensorimotor			
SM1	Fingertip Tapping	SM3	Visuomotor precision-time
SM2	Imitation hand position	SM4	Manual motor sequence
Social perception			
SO1	Theory of mind	SO2	Affect recognition
Visuo-spatial processing			
V1	Design copy	V4	Geometric puzzles
V2	Block construction	V5	Route finding
V3	Picture puzzles	V6	Arrows

The subtests within each domain vary in terms of stimulus presentation modalities (eg., auditory and visual) and type of measure (accuracy/speed, immediate/delayed, recognition/recall). The different subtests as they appear in the scoring form are described below.

The six subtests included in the Attention and Executive Functioning domain are:

A1 Visual Attention (ages 3-16): evaluates visual search requiring crossing out one or two targets amongst a variable number of distractor stimuli;

A2 Design Fluency (ages 5-12): evaluates the ability to generate unique designs by connecting up to five dots presented in structured or random arrays;

A3 Auditory Attention (ages 5-16)and Response Set (ages 7-16): evaluates sustained auditory attention and the ability to shift and update new and complex set of rules involving the inhibition of previously learned responses;

A4 Inhibition (ages 5-16): evaluates the ability to inhibit automatic responses in favour of novel responses and to switch between response types. It is divided into three conditions: naming, inhibition and switching. Both accuracy and speed are obtained for each condition;

A5 Clocks (ages 7-16): evaluates the concept of time by drawing and reading time on analogue and digital clocks;

A6 Animal Sorting (ages 5-16): evaluates concept formation and switching by requiring card sorting into two groups of four cards each using various self-initiated criteria.

A7 Statue (ages 3-6): assesses motor persistence and inhibition by requiring to maintain a body position with eyes closed during a 75-second period and to inhibit the impulse to respond to sound distracters.

The seven subtests included in the Language domain are:

L1 Body Part Naming and Identification (ages 3-4): assesses confrontation naming and name recognition, basic components of expressive and receptive language. For Naming items, the child names the parts of the body on a figure of a child or on his or her own body. For identification items, the child points to corresponding parts of the body on a figure as the examiner names them aloud;

L2 Comprehension of Instructions (ages 3-16): evaluates the ability to understand and carry out verbal instructions of increasing syntactic complexity;

L3 Speeded Naming (ages 3-16): evaluates rapid semantic access by requiring to name an array of pictures or letters and numbers as quickly as possible. Time and accuracy are recorded;

L4 Phonological Processing (ages 3-16): evaluates phonemic awareness by requiring to identify pictures corresponding to given word segments and to create new words by omitting or substituting a syllable or a phoneme;

L5 Word Generation (ages 3-16): evaluates lexical access by requiring to generate in one minute as many words as possible from a given category (animals, food and drinks) or initial letter (F and S);

L6 Repetition of Nonsense Words (ages 5-12): evaluates verbal working-memory by requiring nonsense-word repetition;

L7 Oromotor Sequences (ages 3-12): evaluates oromotor planning by requiring repetition of articulatory sequences and tongue twisters.

The seven subtests included in Memory and Learning domain are:

M1 Memory for Faces (ages 5-16): evaluates face recognition by requiring to identify a previously presented face among three distractors. Memory for Faces Delayed is administered 15 to 25 minutes later;

M2 Word List Interference (ages 7-16): evaluates working memory by requiring repetition of two word lists of increasing length in the same order of presentation;

M3 Memory for Designs (ages 3-16): evaluates visuo-spatial memory by requiring to identify form and position of an abstract design on a grid with 4 to 10 distractors. Content (visual form recognition) and spatial (localization) scores are obtained. Memory for Design Delayed is administered 15 to 25 minutes later;

M4 List Memory (ages 7-12): evaluates episodic memory by requiring to learn a list of words over five trials and recall it after an interference list. List Memory delayed is administered 25 to 35 minutes later;

M5 Memory for Names (ages 5-16): evaluates episodic memory for name-face association over three trials;

M6 Narrative Memory (ages 3-16): evaluates episodic memory by requiring repetition of a story in both free and cued conditions;

M7 Sentence Repetition (ages 3-16): evaluates episodic memory by requiring immediate recall of sentences of increasing length.

The four subtests included in Sensorimotor domain are:

SM1 Fingertip Tapping (ages 5-16): evaluates the ability to imitate a series of finger movements (single and sequences) with the dominant and non-dominant hand. Speed is recorded;

SM2 Imitating Hand Positions (ages 3-12): evaluates visuo-motor planning requiring to imitate finger positions;

SM3 Visuo-motor Precision (ages 3-12): evaluates visuo-motor integration by requiring to draw a line following paths of different widths and spatial complexity. Both accuracy and speed are measured;

SM4 Manual Motor Sequences (ages 3-12): evaluates visuo-motor planning by requiring imitation of a series of hand movements.

The two subtests included in Social Perception domain are:

SO1 Theory of Mind (ages 3-16): evaluates the capacity to predict reactions or behaviours in certain situations. Verbal or pictorial descriptions of several social situations are presented and questions asked that require an understanding of the characters' point of view;

SO2 Affect Recognition (ages 3-16): evaluates the ability to recognize emotional expressions by matching two children’s faces expressing the same emotions among three or more alternatives.

The seven subtests included in Visuo-spatial processing domain are:

V1 Design Copying (ages 3-16): evaluates visuo-motor integration by requiring to copy geometric figures of increasing complexity;
V2 Block Construction (ages 3-16): evaluates constructional praxis by requiring production of three-dimensional constructions of increasing complexity starting from either a three- or a two-dimensional model;
V3 Picture Puzzles (ages 7-16): evaluates figure-ground discrimination by requiring to identify four parts of a larger picture;
V4 Geometric Puzzles (ages 3-16): evaluates mental rotation by requiring to recognize rotated geometric shapes among a series of distractors;
V5 Route Finding (ages 5-12): evaluates mental navigation by requiring to identify the correct path leading to a target on a schematic map;
V6 Arrows (ages 5-16): evaluates line orientation recognition by requiring to identify among an array of arrows the one pointing to a target.

Strengths and limitations of the NEPSY-II

The NEPSY-II remains one of a very small number of tests developed specifically and primarily as a neuropsychological battery for children from 3 to 16 years old (Brooks et al., 2010). There are so few neuropsychological tests normed for preschool and the adolescent age range, thus NEPSY-II fills the gap that occurs for some neuropsychological tests, which often have missing or incomplete norms coverage for this wide age group. The NEPSY-II is one of the few developmental neuropsychological tools available for comparing performance across subtests using updated data on co-normed subtests. As for psychometrical proprieties, the battery has generally high internal reliabilities and respectable test-retest reliabilities for most subtests, and a large concurrent validity is found correlating it with other neuropsychological tests.

As for all neuropsychological tests and batteries, the NEPSY-II has some limitations. It is missing a factor analysis, which would have been helpful for determining whether the test should be seen as a scale containing multiple separate domains, as it is conceptualized and presented in the manual (Titley and D'Amato, 2008). Including reliable clusters of subtests in the form of index scores may indeed have increased the test's clinical utility by yielding higher reliability scores. Other limitations of the NEPSY-II concern the complex and lengthy administration (4-6 hours). Firstly, the large number of subtests can make it challenging to comprehend, to interpret, and to utilize the vast amount of psychometric information presented in the technical manual. Secondly, scoring can be complex for some subtests, with numerous primary, process, and contrast scores, as well as behavioural observations. Thirdly, similar to any other neuropsychological battery,

clinicians should be cautious about the risk of over-interpreting isolated low scores because of the high number of scores generated by the battery (Brooks et al., 2010).

MRIs studies of brain development and relation to cognitive functions

The need to increase the knowledge on normal brain development as a foundation for cognitive and neuropsychological functioning is crucial in order to accurately detect and understand the mechanisms of neurodevelopment disorders. In the last years, several MRI studies on normal brain structural development and its relations to cognitive functions have described these relationships. The human brain has a particularly protracted maturation, with different tissue types, brain structures, and neural circuits having distinct developmental trajectories undergoing dynamic changes throughout life. Longitudinal MR scans of typically developing children and adolescents demonstrate increasing white matter volumes and inverted trajectories of gray matter volumes with peak sizes occurring at different times in different regions.

Recent longitudinal data show that cortical gray matter volumes more than doubles (108%) during the first year of life, with lesser increase (19%) during the second year (Gilmore et al., 2012). Cortical expansion appears to be region specific, paralleling cognitive and functional development at different stages: relatively more expansion in the first year is seen in parts of superior temporal and parietal, post-central and occipital cortices, perhaps reflecting rapid development of sensory functions (Li et al., 2014). In the second year, particular expansion is seen in superior frontal, inferior temporal, and inferior and superior parietal cortices, involved in motor planning and higher-order visuo-spatial, sensory, and attentional processing (Li et al., 2014).

White matter microstructure also shows faster rate of change in first than second year, with rapidly increasing fractional anisotropy and decreasing radial and axial diffusivity (Geng et al., 2012; Short et al., 2013). Again, region-specific maturational patterns are observed: colossal tracts exhibit larger radial diffusivity changes in the first year. Motor and sensory tracts are more mature at birth and develop more slowly (Geng et al., 2012), in correspondence with gray matter volume in sensory-motor regions. A leftward development of arcuate fasciculus has been found in the first year, suggestive of emerging language-related lateralization differences (Geng et al., 2012). Multimodal and network approaches show maturation from a local to a distributed organization (Fair et al., 2009; Lee et al., 2013; Gao et al., 2013). Both the dorsal attention and default-mode network start from isolated region in neonates but evolve to synchronized networks at one years of age (Gao et al., 2013). This pattern of development is enhanced, but less dramatic in the second years, echoing structural maturation (Gilmore et al., 2012; Li et al., 2014).

A number of previous studies have pointed to increases in cortical thicknesses well into preschool and school age (Shaw et al., 2008; Giedd et al., 2012), followed by later maturation thinning. However, a recent report indicates monotonous decrease in cortical thickness in the age range 3-21 years (Brown et al., 2012b), while cortical surface area expands up until the age of 12 years (Brown et al., 2012a). The phase of cortical thinning which dominates adolescence might reflect the use-dependent selective elimination of synapses (Huttenlocher et al., 1997) and the proliferation of myelin into the peripheral cortical neuropil (Sowell et al., 2004) that could refine neural circuits, including those supporting cognitive abilities (Knudsen, 2004). Thus, regional volume increases and decreases are ongoing simultaneously in different parts of the cortex, including increases in temporal and prefrontal cortices in preschool years and decreases in occipital and primary somatosensory areas (Brown et al., 2012b).

These maturational cortical volume reductions and thinnings are strongly associated with cognitive development. Cortical reductions in fronto-parietal networks, indeed, have been related to improvement in working memory and executive function in the age range 8-22 years (Tamnes et al., 2013). However, indices of general intellectual ability and executive function have been positively correlated with the gray matter volume in temporal, frontal, cingulum, and precuneus as well as early visual area gray matter in a group of healthy children aged 6-18 years (Ziegler et al., 2013). These relationships appear to vary with age (Shaw et al., 2008), with negative correlations between gray matter volumes and executive function performance during development, suggesting neuroanatomical changes as pruning, dendrite changes and myelination processes. The thinner parietal cortices, similarly, have been found during the development and have been associated with better verbal learning and memory, visuo-spatial functioning and problem solving in adolescence (Squeglia et al., 2013).

From the knowledge on normal structural brain development, the long-term impact of early events during brain maturation on cognition, such as the congenital brain lesions in cerebral palsy, is an area of great topical interest given its important contribution to clinical assessment and early rehabilitative intervention.

New rehabilitation approaches for the study of neurofunctional reorganization: CogMed, a working memory home-based training

Cognitive tele-rehabilitation in developmental disorders

Tele-rehabilitation is rehabilitative therapy, assessment, or training outside the laboratory or the hospital through the use of information and communication technology (Rosen, 1999). The clinical use of the tele-rehabilitation, or home-based, improves the quality of clinical services, by facilitating access to therapy helping to break geographical barriers, to extend the therapeutic processes beyond the hospital, as the child's home, and to improve costs/benefits ratio (Cantagallo, 2014).

The efficacy of cognitive tele-rehabilitation in developmental disorders has been confirmed by several international and national studies in the literature (Olesen e coll., 2004; McNab et al., 2009; Holmes et al., 2009; Bellander et al., 2011; Franceschini et al., 2013; Tressoldi et al., 2012). These studies underline the significant improvement of different cognitive processes, as working memory (Olesen et al., 2004; McNab et al., 2009; Holmes et al., 2009; Bellander et al., 2011), visuo-spatial attention (Franceschini et al., 2013) and literacy abilities (Tressoldi et al., 2012) after home-based trainings. Some of the important factors which strongly influence the efficacy of tele-rehabilitation are: the intensity of the training, that is the need to exercise the trained cognitive process every day, its adaptability adjusting trial difficulties based on child's performances, and the child's and family's motivation.

Some studies have also investigated the effect of tele-rehabilitation on neurofunctional reorganization (Olesen et al., 2004; McNab et al., 2009; Brehmer et al., 2011) underlying the strong influence between this new rehabilitative approach and advanced neuroimaging techniques, such as fMRI, DTI or high density EEG. Indeed, the developmental neuro-plastic reorganization, defined as ''neuronal recycling'' (Dehaenne, 2009), is crucial for cognitive learning and brain maturation consisting of the putative mechanism by which a novel cultural object encroaches onto a pre-existing brain system. The term "recycling" is referred to a short-term change taking place over only a few months for a partial or total invasion of a cortical area initially devoted to different functions, so it is a form of re-orientation or re-training transforming an ancient function, evolved for a specific domain, into a novel function that is more useful in the present cultural context. According to this neurofunctional hypothesis, the human brain would be able to accommodate a broad range of new functions through learning.

CogMed working Memory training

Working memory

Working memory, inhibition and cognitive flexibility are three core Executive Functions, a family of top-down mental processes needed to concentrate and pay attention, when going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible (Miyake et al., 2000; Letho et al., 2003; Diamond, 2012).

The most widely used model of working memory (WM) includes several components: the central executive, phonological loop, visual-spatial sketchpad, and episodic buffer (Baddeley et al., 1994, 2000). The central executive is an attentional control system involved in several processes such as the selection and execution of strategies, retrieval of information from long-term memory, monitoring of input, simultaneously storing and processing of information, and the coordination of the other components of the WM system. The visual-spatial sketchpad involves temporary storage and rehearsal of visual and spatial information, while the phonological loop involves storage and rehearsal of phonological and auditory information. The episodic buffer – a temporary storage system that is responsible for the integration of information from a variety of sources – is the third slave system (Baddeley, 2000).

Working memory is the ability to hold information in mind and mentally working with it (Baddeley et al., 1994, Smith et al., 1999) and is important for complex cognitive activities. It is necessary for making sense of written or spoken language, for mentally reordering items (such as reorganizing a to-do list), for translating instructions into action plans, incorporating new information into thinking or action plans (updating), considering alternatives, and mentally relating information to derive a general principle or to see relations between items or ideas (Diamond et al., 2011). Several researches documented the role of working memory in academic achievement, such as math and reading (Holmes et al., 2009; English et al., 2010; Van de Weijer-Bergsma et al., 2015), because it requires the child to pay attention to instructions or information, to hold information in mind, and to integrate that information so as to derive meaning from it.

Neurofunctional brain development of working memory

The ability to hold information in mind develops very early. Even infants and young children can hold one or two things in mind for quite a long time (Diamond 2002; Cowan, 2012). It was Piaget who first observed that infants younger than 7 months fail to accurately retrieve a hidden object after a short delay period if the object's location is changed from one where it was previously and successfully retrieved. These infants, indeed, often reach to the hiding location where the object was found on the immediately preceding trial, executing a pattern of error called "A not B" (Piaget, 1954) due to the failures to understand that objects retain their existence and permanence when moved from view. Between 7 and 9 months, infant begin to succeed in the task at successively longer delays of 1 to 5 seconds (Diamonds, 1985 and 2001) but continue to make the A not B error up to around 12 months if the delay between hiding and retrieval is incremented (Diamond, 1985).

Non-invasive imaging methods have been used to link maturation of the prefrontal cortex to development of infant's performances in the A not B task. Increases in frontal EEG responses in infants have been shown to correlate with the ability to respond successfully over longer delays in delayed response tasks (Fox et al., 1990; Bell et al., 1992) and changes in blood oxygenation in the prefrontal cortex, by optical imaging (NIRS), have been found correlated with behavioural demonstration of object performance (Baird et al., 2002). In Diamond's view (1991), the emergence of the ability to demonstrate knowledge about an object's permanence results from the maturation of the dorsolateral prefrontal cortical region between the ages of 5 and 12 months. Diamond proposed that this region is important when the child has both to retain information over spatial delays and inhibit prepotent responses. This suggests that Piaget's observations about object permanence reflect the state of underlying neural mechanisms (Johnson, 2011). The maturational approach to prefrontal cortex development has also been extended to later childhood and adolescence. Several fMRI studies (Klingberg, 2006) documented that dorsolateral prefrontal cortex is involved in working memory in both children and adults, but also show that it is activated as part of a network also involving the intraparietal cortex. These studies show that stronger activation of the fronto-parietal network is related to greater working memory capacity, and that activation of the network also increases with age (Klingberg et al., 2002a). Development of white matter tracts connecting the frontal and parietal regions seems to play a role in these processes: maturation of these tracts are related to working memory performance and to the degree of cortical activation in the frontal and parietal gray matter (Olesen et al., 2003). At a cellular level, computation modelling indicates that stronger synaptic connectivity between prefrontal and parietal regions, and not faster transmission of neural signals or stronger connections within each region, can by itself account for observed changes in brain activity associated with the development of working memory in childhood (Edin et al., 2007).

Evidence-based cognitive training

Recent reviews of executive function interventions underlined that working memory and attentional control must be continually challenged and may be considered as "tools for learning", favouring the acquisition of skills in other cognitive domains (Diamond et al., 2011; Spencer-Smith et al., 2015; Wass et al., 2012; Wass et al., 2015). One of the most commonly used training to improve working memory in the literature is CogMed program (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden) developed by Klingberg and collaborators (2002b). The efficacy of CogMed has been demonstrated through a credible body of scientific evidence. Blinded, randomized and controlled trials were conducted to compare adaptive CogMed training to both non-adaptive (placebo) CogMed training (Chacko et al., 2014; Dunning et al., 2013; Green et al., 2012; Holmes et al., 2009; Klingberg et al., 2002b, 2005) and non-adaptive commercially available video games (Thorell et al., 2009) finding significant differences across them in favour of the adaptive CogMed condition.

The impact of CogMed Working Memory Training has been shown on two levels of assessment: brain imaging and neuropsychological tests. Neuroimaging studies, using PET and fMRI scans in healthy adults, revealed that improvements in working memory after CogMed program are associated with changes in the density of cortical D1 dopamine receptors (McNab et al., 2009) and with increased activation in frontal and parietal regions (Olesen et al., 2004; Westerberg et al., 2007). However, another fMRI study documented a larger activation decrease in frontal, temporal, and occipital regions during high-load working memory tasks in the adaptive CogMed condition respect to control. These results suggested intervention-related increases in neural efficacy, as less neural energy is being required to attain the same working memory performance level post training (Brehmer et al., 2011). Thus the relationship between activation changes and performance after CogMed intervention is still an open issue.

Beyond imaging data, the neuropsychological findings in CogMed studies document the improvement in working memory abilities and in non-trained cognitive processes both in clinical and typical populations at different age ranges, in pre-school (Thorell et al., 2009; Bergman et al., 2011; Grunewaldt et al., 2013), school-aged children (Klingberg et al., 2002; Green et al., 2012), in adolescents (Løhaugen et al., 2011) and adults (Brehmer et al., 2012; Gropper et al., 2014). In 2009, Thorell and co-workers found that it was feasible to train 4 and 5 year olds and that training effects transferred to non-trained working memory tests. These findings are supported by significant improvements in visuo-spatial working memory in a study of typically developing pre-school children (Bergman et al., 2011), as well as improved auditory attention, phonological processing, visual and verbal memory and learning, and sentence repetition in pre-schoolers born at very low birth weight (Grunewaldt et al., 2013). Klingberg and co-authors (2002, 2005) and Green and co-

workers (2012) observed significant effects on the span-board, a non-trained assessment of verbal and visuo-spatial working memory, in children with ADHD, aged 7 to 15 years. In 2011, Løhaugen and co-workers found that adolescents (ages 14 to 15 years) born at extremely low birth weight (ELBW) improved in both visuo-spatial and verbal WM immediately after CogMed training and at 6 a month follow-up compared to their baseline performance. This significant training effect was also observed in a healthy born, age-matched comparison sample. Both young and older adults have also shown improved working memory after CogMed training, revealing that adaptive training of typically functioning 20 to 30 and 60 to 70 year olds led to significant improvements on non-trained verbal (digit span forward) and visuo-spatial (span board backward) WM tests (Brehmer et al.,2012).

In studies that have included a long-term follow-up, increases in WM capacity and improved behaviour have been observed from two months to one year post-training (Klingberg et al., 2005; Dahlin et al., 2011; Brehmer et al., 2012). More recent research and clinical evidence has shown gains in working memory sustained for up to 12 months post-training. Dunning and co-workers (2013) demonstrated in a randomized, placebo controlled study that school-aged children with low working memory who trained with CogMed maintained improvements in verbal working memory on the Automated Working Memory Assessment, as well as on an classroom-based task of working memory ability (sentence counting) at one year follow-up.

CogMed method

CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden) is an home-based software to improve working memory abilities. It is available in three on-line versions depending on age, CogMed JM (for pre-schoolers from the age of four), CogMed RM (for children and adolescences), CogMed QM (for adults). All three online versions contain a number of exercises that vary automatically during the training period and each of them must be completed in order to finish the day's training session. In order to train working memory as efficiently as possible, the training must consistently be set on a challenging level. The difficulty level, indeed, is adjusted automatically based on user's capacity. Training is planned to be intensive, thus the CogMed standard protocol provides 25 home-based sessions over 5 weeks, each lasting 50 minutes in CogMed RM and 30 minutes in CogMed JM.

For CogMed training the presence of a training aide is necessary, a parent or adult who can support and guide the user thought the home-based training period, and a CogMed coach, the clinician who follows the user for all the training period. The CogMed coach explains the principles and the characteristics of the program to the user and his/her family, gives extra motivation when in

difficult situations and daily monitors the training using CogMed training web, a web site where the development of the training program can be viewed from graphs or indices. The coaching method consists of four important steps:

1. *Initial interview*: to judge whether the user is a suitable candidate for training or not and to get to provide the user and his/her family the information needed to decide whether or not to start the training.

2. *Start-up session*: the CogMed coach plans and structures the training together with the user and training aide to establish a common set of expectations on the training and some guidelines for carrying it out. It consists of the following steps:

- To describe working memory and its impact on daily life activities;
- To present the program and its characteristics, trying some exercises of the CogMed demo version;
- To establish five positive rewards for the end CogMed weekly sessions;
- To plan the training, the five training days and the coach's calls;
- To try the first CogMed session in the laboratory and give advice to continue at home;
- To fill out questionnaire and rating scales by parents relative to the child's performance.

3. *Weekly Coach Call:* throughout the training period the CogMed Coach makes five weekly calls to the user and training aide to take feedback of the home-based training and to give advice also based on daily monitoring of child's progress using CogMed Training Web.

4. *Wrap-up session:* At the end of the 25 sessions, the CogMed coach makes a brief interview to take final feedbacks by user and training aide, summarizes the results of the training, based on CogMed Training Web and, if used, neuropsychological pre- and post- training assessments, and give the CogMed diploma.

Study 1

Beyond visuo-spatial deficits in children with periventricular leukomalacia: Neuropsychological profile at the NEPSY-II and neuroanatomical correlates

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Beyond visuo-spatial deficits in children with periventricular leukomalacia: Neuropsychological profile at the NEPSY-II and neuroanatomical correlates

Introduction

Periventricular leukomalacia (PVL) is a form of white matter brain injury typically affecting preterm born infants, and it is the most common neuropathological pattern underlying Cerebral Palsy (CP) (Rosenbaum et al., 2007). Periventricular leukomalacia may determine the disruption of several white matter pathways lying close to the lateral ventricles, e.g. the corticospinal tract, mostly resulting in spastic motor disorders, or the optic radiations, resulting in visual function deficits. According to lesion site or extension (from the periventricular layer to the middle white matter), several associative fibres may be disrupted, leading to neuropsychological deficits (Uggetti et al., 1996; Cioni et al., 2000; Fazzi et al., 2009; Guzzetta et al., 2010; Pavlova et al., 2013).

General cognitive abilities are usually within low average-borderline range in children with PVL, but a large discrepancy is consistently reported between Verbal and Performance Intelligence Quotients, with only the latter being in the deficit range (Fedrizzi et al., 1993; Ito et al., 1996; Fazzi et al., 2009; Pavolva et al., 2013).

Significant deficits in visuo-spatial skills have been extensively described in this clinical population also early in development (Koeda et al., 1992; Jacobson et al., 1998; Lanzi et al., 1998; Fazzi et al., 2009; Pueyo et al., 2009), with associated mathematical disabilities reported at school age in some studies (Pavolova et al., 2009; Jenks et al., 2012).

Whereas the literature on cognitive development in children with PVL has been mainly focused on describing deficits especially in the visuo-spatial domain, less is known on the integrity and the developmental trends of other cognitive functions (Shatz et al., 2001; Pirila et al., 2004; White et al., 2005; Korkman et al., 2008; Pueyo et al., 2009; Pirila et al., 2011).

Few studies have focused on attention and executive functions in children with bilateral CP. Schatz and collaborators (Shatz et al., 2001) found impaired ability in quickly shifting visual attention from a novel position to another previously observed in children with perinatal lesions resulting in spastic diplegia. Pirila and co-workers (Pirila et al., 2004; Pirila et al., 2011), reported deficits in visual and auditory attention, in the inhibition of previously learned auditory responses, and in problem solving tasks, underlying the influence of preterm birth and birth weight on executive functioning in children with bilateral spastic CP. White and Christ (White et al., 2005) found, in spastic bilateral CP, inefficient clustering during word learning suggestive of an impairment of the active component of memory mediated by the pre-frontal cortex. Korkman and collaborators (Korkman et al., 2008) confirmed in the same population a deficit in attention and

inhibition also in pre-school age. Bottcher and co-workers (Bottcher et al., 2009) found impaired speed and accuracy in inhibition and switching tasks in bilateral CP.

Most of these studies did not test various cognitive domains at the same time point in the same patient and combined tests with different standardization samples, thus making it hard to clearly define the neuropsychological profile of bilateral CP due to PVL.

In addition to scant research on the comprehensive neuropsychological functioning of children with PVL, also the neuroanatomical correlates of neuropsychological strengths and weaknesses have been rarely investigated. Some studies, by means of cranial ultrasound, did not find any correlations between lesion characteristics and neuropsychological data (Pirila et al., 2004; Korkman et al., 2008). Research with magnetic resonance imaging (MRI), the gold standard for the study of brain injury in CP, has focused mainly on the association between the extent of PVL and visuo-spatial functions, confirming the strong relationship between the extension of periventricular white matter damage to parietal and occipital regions and the degree of impairment of visual functions, including high-level skills (Ito et al., 1996; Van den Hout et al., 2004; Fazzi et al., 2004; Pavolva et al., 2007; Pagliano et al., 2007; Guzzetta et al. 2010). Advanced MRI techniques such as diffusion tensor imaging found correlations between alterations of connectivity in PVL and low intelligence but not with specific neuropsychological functions (Wang et al., 2013).

The main aim of the present work was to verify whether PVL, which represents a homogeneous type of lesion in the CP population, may be associated with specific patterns of neuropsychological functioning and, if so, to identify their specific neuroanatomical correlates.
Thus, this study is the first to concurrently analyze:

a) the profile of children with PVL across different neuropsychological domains with a comprehensive, co-normed, and multi-domain neuropsychological battery (NEPSY-II, Korkman et al., 2007). This battery covers an extensive age range (3-16 years) and a wide range of neuropsychological domains (Attention/Executive Functioning, Language, Memory and Learning, Social Perception, Sensorimotor, and Visuo-spatial Processing). The NEPSY-II allows to overcome the methodological limits of cognitive assessment with test standardized on different normal populations.

b) the association between neuropsychological strengths and weaknesses and lesion characteristics, analyzed with a novel and reliable semi-quantitative scale for classification of structural brain MRI (Fiori et al., 2014).

Material and Methods

Participants

Twenty children (10 females) with PVL (mean age 9y 1mo, SD 2y 7mo, range 5y 1mo-15y 9mo) and a mean gestational age at birth of 32 weeks (range 29-41 wks) were selected from a larger sample of children with CP referred in the years 2012-2013 to the Department of Developmental Neuroscience of Stella Maris Institute. Children were selected according to the following inclusion criteria: a) neuroradiological diagnosis of PVL documented at brain MRI performed after age 2 years; b) levels I to III at the Manual Ability Classification System (MACS, Elliasson et al., 2006); c) absence of drug-resistant epilepsy; d) absence of a psychiatric disorder diagnosis or sensory deficits that preclude testing; e) Verbal Intelligence Quotient >80, as assessed in the last year prior to recruitment by WPPSI-III (Wechsler et al., 2008; WISC-III (Wechsler et al., 2006) or WISC-IV (Wechsler et al., 2012). The PVL group was compared to 40 healthy children (Control group) matched 2:1 for age and gender (Haviland et al., 2007), who were randomly selected from the Italian standardization sample (Urgesi et al., 2011). The PVL group was assessed with NEPSY-II in six one-hour sessions by the same examiner. All children were native Italian speakers.

The research project was approved by the Ethical Committee of Stella Maris Institute (n° 07/2012). Written consent for participation was obtained from all participants' parents who also gave informed consent to publication of results.

Gross motor skills were assessed with The Gross Motor Classification System (GMCS, Palisano et al., 1997). Children were classified according to five motor levels: walk without restriction (level I); walk without assistive devices but limitation in walking outdoors (level II); walk with assistive mobility devices (level III); self-mobility with limitations (level IV); self-mobility severely limited even with use of assistive technology (level V). Manual ability was classified according to MACS (Eliasson et al., 2006), as indicated above.

Visual functions were assessed for the presence of deficits in the following areas: stereopsis, ocular motility, visual field and acuity. Visual functions were classified as no deficit, mildly impaired (maximum two deficits), severely impaired (three or more deficits).

Magnetic resonance imaging was classified according to a novel semi-quantitative scale (Fiori et al., 2014) by a child neuropsychiatrist with a strong neuroimaging background, who was blinded with respect to patients' neuropsychological findings. Scans were suitable for quantitative scoring in 16 children.

The semi-quantitative scale was developed for classification of brain lesion severity on structural MRI in children with CP, based on visual approach. The semi-quantitative scale demonstrated high inter-rater reliability and intra-rater reliability (Fiori et al., 2014). Brain lesion is

graphically represented onto a graphical six-slices template. Raw scores for each lobe, subcortical structures (basal ganglia, thalami and brainstem), corpus callosum and cerebellum are systematically calculated. A global score and several MRI subscores (ordinal variables) derive from the scoring procedure, with higher scores representing more severe pathology. The lobar scores (parietal, temporal, occipital and frontal) are the sum of the raw scores resulting from the involvement of bilateral white matter (periventricular and middle) and cortico-subcortical layers (bilateral maximum score 6). The hemispheric score is the sum, for each hemisphere, of the lobar scores (maximum score 12). The corpus callosum score is the sum of anterior, middle and posterior portions subscores (maximum score 3). The basal ganglia and brainstem score is the sum of the bilateral subscores of different subcortical structures (basal ganglia, thalamus, brainstem and posterior limb of the internal capsule, maximum score 10). The global score is the sum of bilateral hemispheric, basal ganglia, brainstem and corpus callosum scores (maximum score 40).

Neuropsychological Assessment

Cognitive functioning was assessed with the Italian adaptation of NEPSY-II, a comprehensive neuropsychological battery developed for the evaluation of children aged 3 to 16 years (Korkman et al., 2007). The NEPSY-II is becoming an internationally recognized measure for neuropsychological assessment in children and adolescents (Pirila et al., 2004; Korkman et al., 2008; Olivieri et al., 2011; Parisi et al., 2012; Narzisi et al., 2013a; Korkman et al., 2013; Barron-Linnankoski et al., 2015). The Italian NEPSY-II consists of 33 subtests divided into six cognitive domains: Attention/Executive Functioning, Language, Memory and Learning, Social Perception, Sensorimotor, and Visuo-spatial Processing. The number of subtests in each domain varies as a function of age range. The subtests within each domain vary in terms of stimulus presentation modalities (eg., auditory and visual) and type of measure (accuracy/speed, immediate/delayed, recognition/recall, content/spatial). For the purpose of further differentiating strengths and weaknesses in the neuropsychological profile of PVL, the Memory and Learning domain was divided in verbal and visuo-spatial components (Verbal Memory and Visuo-spatial Memory), thus a total of seven domains were considered.

The description of each subtest as they appear in the scoring form is reported in the "Structure and purpose of NEPSY-II" section included in the PhD thesis introduction. If not otherwise specified, raw scores were based on response accuracy.

Statistical analysis

All raw scores for each NEPSY-II subtest were expressed as scaled scores (mean 10; SD 3) with respect to the age-matched normative sample values (Urgesi et al., 2011). For missing data,

casewise deletion was applied. Scaled scores included also negative numbers because they were derived from the normative values with no approximation at the low or high extremes. Seven mean domain scores were calculated by averaging the scaled scores of all subtests included in each domain.

Mixed ANOVAs were used to verify group effects and group/domain interactions at NEPSY-II.

Two-tailed t-tests were used to compare: a) verbal and non-verbal discrepancy at the Wechsler Scales in the PVL group; b) post-hoc differences in the mean domain and single subtest scores between PVL and Control groups; c) performance of the PVL group for different measures within each subtest (accuracy/speed and content/spatial), where applicable. For multiple t-test comparisons, the Bonferroni's correction was applied.

Cohen's d was calculated to determine the effect size of the differences on the mean domain and single subtest scores between PVL and controls.

The neuroanatomical findings and neuropsychological correlates were examined with the following analyses: a) non-parametric related comparisons (Friedman and Wilcoxon) on lobar and hemispheric median scores; b) chi-square test on the association between presence/absence of lesion in the different neural structures (anterior, middle and posterior corpus callosum portions and basal ganglia); c) bi-variate non-parametric correlations (Spearman) between the MRI ordinal scores and NEPSY-II mean domain scores; d) two-tailed t-tests and chi-square test on NEPSY-II performance according to the presence/absence of lesions in the different neural structures.

Results

Clinical characteristics of the PVL group

All the children with PVL received a diagnosis of spastic bilateral CP, with more impaired lower (GMFCS) than upper limbs (MACS, inclusion criterion).

Motor, visual and cognitive functions are reported in Table 1.

Table 1

Clinical characteristics of PVL group

	Sex	Age (y;m)	GA	Motor Function		Visual Function deficit	Intelligence	
				GMFCS Levels	MACS Levels		Verbal*	Non-verbal*
S1	M	8;5	30	II	II	Mild	103	59
S2	M	8;3	31	III	I	Mild	97	77
S3	F	6;1	29	IV	III	Mild	104	46
S4	F	9;1	31	II	II	Severe	104	67
S5	M	9;0	36	II	I	Mild	82	71
S6	F	11;2	34	II	II	Mild	82	52
S7	F	12;3	34	II	II	Mild	98	93
S8	M	9;1	29	IV	III	Mild	88	54
S9	M	5;1	31	III	II	Mild	84	87
S10	F	13;5	29	IV	II	No	92	74
S11	F	10;8	32	I	II	Mild	82	87
S12	M	15;9	41	II	I	Mild	92	82
S13	F	8;1	34	IV	I	Mild	102	100
S14	M	10;5	28	I	I	Mild	102	115
S15	F	5;4	32	II	I	No	100	80
S16	F	9;7	28	III	II	Mild	99	89
S17	M	7;9	32	II	II	Mild	100	62
S18	M	8;2	30	II	II	Mild	100	82
S19	M	6;5	32	I	I	Mild	100	76
S20	F	6;3	32	III	II	Mild	100	89

Notes: GA, gestational age; GMFCS, Gross-Motor Function Classification System; MACS, Manual Abilities Classification System; Verbal*, Verbal IQ (WISC-III, WPPSI-III) or Verbal Comprehension Index (WISC-IV); Non-verbal*, Performance IQ (WPPSI-III) or Perceptual Organization Index (WISC-III) or Perceptual Reasoning Index (WISC-IV).

At gross motor functioning assessment (GMFCS), three children were classified at Level I, nine at Level II, four at Level III and four at Level IV, and at MACS seven children were classified as Level I, 11 at II and two at III. Visual functions were mildly impaired in the majority of children (17/20); one child had severe visual deficits, two normal visual functions.

At the Wechsler scales, verbal intelligence was significantly higher than non-verbal (t(19)=4.6, p<.001) and the discrepancy reached statistical significance in 16 out of 20 children with respect to the Wechsler scale normative data (p<.05). The correlation between non-verbal intelligence and degree of visual impairment was not significant (rho(19)= -.34, ns).

Neuropsychological profile at the NEPSY-II

Periventricular leukomalacia and Control groups were compared on mean domain scores (Table 2).

Mixed ANOVA revealed significant lower performance in PVL than in Control groups (F(1, 57)=67.17, p<0.001) and a significant interaction between group and domains (F(6, 57)=31.08, p<0.001). Post-hoc comparisons revealed that the PVL group performed significantly worse than controls, with a large effect size between groups, in Sensorimotor, Visuo-spatial Memory, Visuo-spatial Processing, Attention/Executive Functioning and Social Perception domains while no significant differences emerged in Language and Verbal Memory domains.

Table 2

Differences between PVL and Control groups at NEPSY-II domains

NEPSY-II domains	PVL Group Mean(SD)	Control Group Mean(SD)	CI (95%)	t	df	*p*	Cohen's d
Attention/Executive Functioning	5.6(3.7)	10.2(1.3)	5.9/3.3	7.13	58	<.001*	-1.5^
Language	8.7(1.9)	9.7(1.8)	2.0/0.0	1.95	58	.056	-.3
Verbal Memory	10.9(1.6)	9.8(1.9)	-0.1/-.2	- 27	58	.027	.4
Visuo-spatial Memory	5.2(3.4)	10.3(1.7)	6.4/3.7	7.65	58	<.001*	- 7^
Sensorimotor	3.6(4.1)	10.4(1.5)	8.2/5.3	9.23	57	<.001*	-.3^
Social Perception	7.7(2.9)	10.6(2.0)	4.3/1.6	4.54	57	<.001*	-.9^
Visuo-spatial Processing	4.6(3.8)	10.1(1.6)	6.9/4.1	7.94	58	<.001*	-.8^

Notes: CI, Confidence Interval of the difference; *Significance after Bonferroni's Correction (p < .007); ^large effect size (Cohen's d > |.8|)

Within the PVL group, for the purpose of the study, performance in each domain was classified into three categories according to scaled scores: deficit (scaled scores 1 to 3), borderline (4 to 6) and average (>7). The distribution of impaired performance, comprising deficient or borderline functioning, revealed that the great majority of children were impaired in Visuo-spatial Processing and/or Visuo-spatial Memory domains (18/20) and in the Sensorimotor domain (15/20). Many children were also impaired in the Attention/Executive Functioning (11/20) and Social

Perception (8/20) domains. Language and Verbal Memory domains were in the average range in 19/20 children (Figure 1).

Figure 1

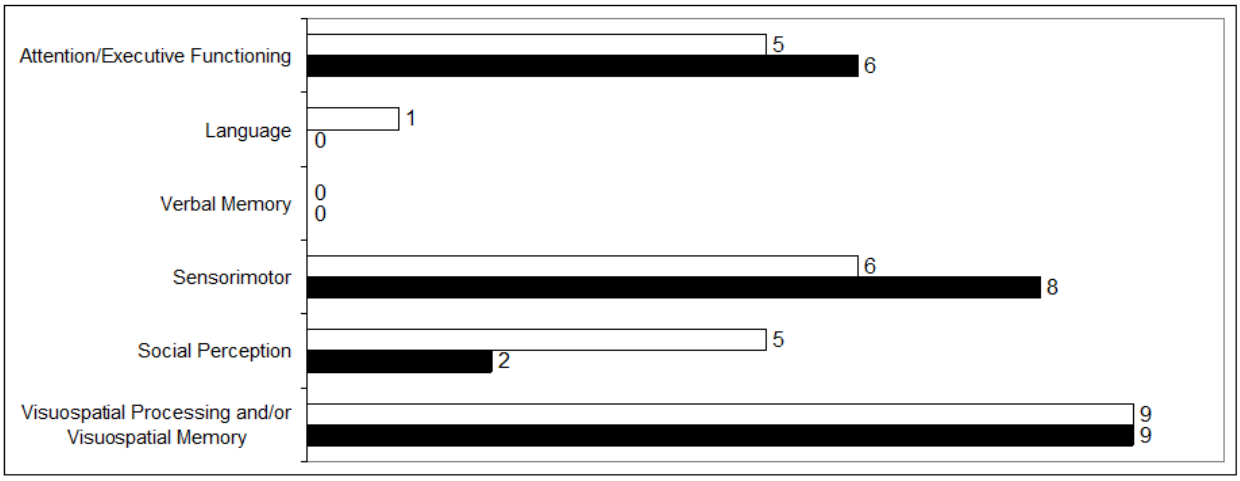

Figure 1: Number of PVL children with performance in the borderline (white bar) or deficit (black bar) range at the NEPSY-II domains.

Figure 2

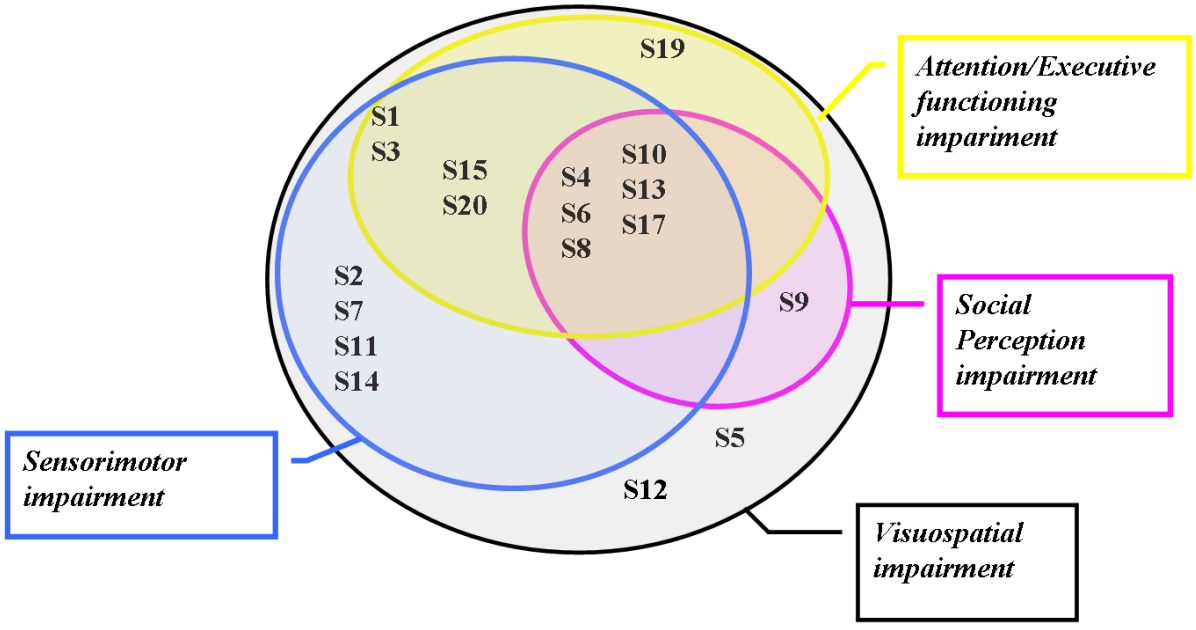

Figure 2: PVL children (n=18) grouped according to impaired performance in one or more NEPSY-II domains. Each set includes children with Visuo-spatial (black circle), Sensorimotor (cyan circle), Attention/Executive Functioning (yellow circle) or Social Perception (magenta circle) impairment.

Among the 18 children with impaired performance in Visuo-spatial Processing and/or in Visuo-spatial Memory domains, two did not display any another associated impairment, six showed one additional impaired domain and 10 had impaired performance in two ore more additional domains. Among the 11 children with Attention/Executive Functioning impairment, nine were impaired also in Sensorimotor and six also in Social Perception domains (Figure 2).

The association between the presence of Attention/Executive Functioning impairment and performance in the other NEPSY-II domains was investigated by mixed ANOVA, using the presence/absence of Attention/Executive Functioning impairment as between subjects variable, and the other NEPSY-II domains as within subjects variables. Although the two groups were equivalent for age (t(18)=-1.36, ns), gestational age (t(18)=.25, ns) and GMFCS level (Mann-Whitney Z=-.28, ns), the group effect was significant (F(1, 17)=13.28, p<.005) and no interaction with domains was found. The PVL group with impaired Attention/Executive Functioning (n=11) had lower performance in all the other NEPSY-II domains with respect to the PVL group without such impairment (n=9) (Figure 3).

Figure 3

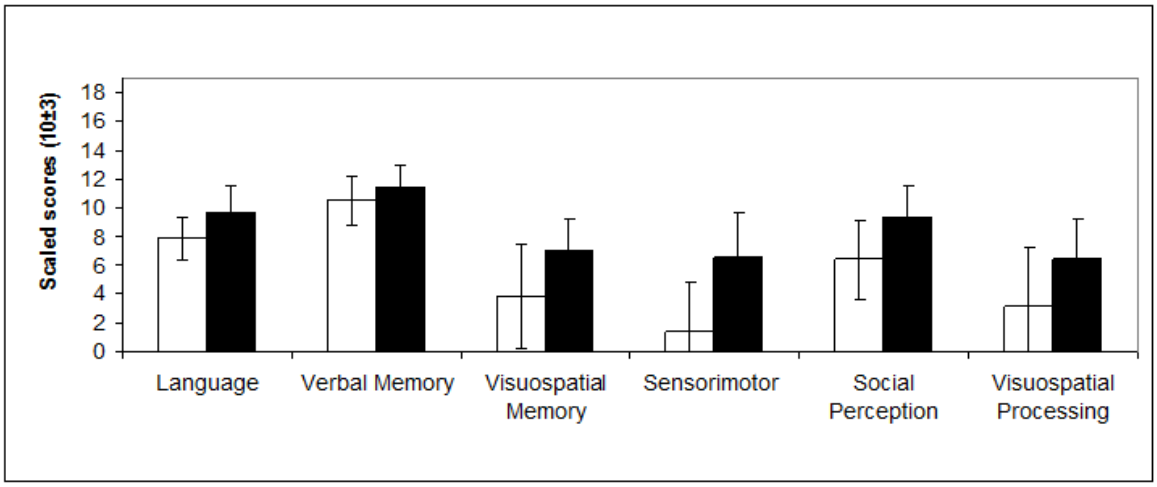

Figure 3: NEPSY-II domains performance according to presence (white bar) or absence (black bar) of impairment in the Attention/Executive functioning domain.

The differences between PVL and Control groups in subtest scaled scores and in the different measures within each subtest are reported in the Table in the Supplementary Material.

Within the Attention/Executive Functioning domain, children with PVL displayed significantly worse performance than the Control group, with a large effect size between groups, in Visual Attention (A1), Design Fluency (A2), Auditory Attention (A3) and Inhibition (A4) subtests.

Within the PVL group the different measures of the Inhibition subtest revealed greater deficits in speed than in accuracy ($t(19)=-4.58$, $p<.001$).

In the Language and Verbal Memory domains, PVL performance at the Phonological Processing subtest (L4), tapping verbal working memory and phonological awareness, was significantly lower than controls, while in some subtests children with PVL performed better than controls, although not significantly.

Within the Visuo-spatial Memory domain, significantly lower scores were found in the Memory for Design subtest (M3) in PVL than in controls, with more efficient content than spatial recognition in the PVL group for both immediate ($t(19)=4.36$, $p<.001$) and delayed ($t(19)=4.37$, $p<.001$) conditions.

In the Sensorimotor domain, performance at the Imitation Hand Position (SM2) and Manual Motor Sequences (SM4) subtests was significantly lower in PVL with respect to controls and in the Visuomotor Precision subtest (SM3) children with PVL were better in speed than in accuracy ($t(13)=3.84$, $p<.005$).

In the Social Perception domain, Theory of Mind (SO1) was significantly impaired in PVL with respect to the Control group.

In the Visuo-spatial Processing domain, performance at all subtests was significantly impaired both in visuo-perceptual and in visuo-constructional tasks as it can be seen from the wide discrepancy between scaled scores (Table in Supplementary Material).

Neuroanatomical findings and correlates

The neuroanatomical classification at the semi-quantitative scale was applied to 16 brain MRIs (performed at a mean age of 5 years). The lobar scores (parietal, temporal, occipital and frontal) derived only from the involvement of bilateral white matter (periventricular and middle), since no child showed any damage in cortico-subcortical layers.

Table 3

MRI lesion classification at the novel semi-quantitative scale in the PVL group

Scores	Frequency of lesion	Severity of lesion	
		Median	min-max
Parietal score	16/16	4.0	3.5 - 4 [0- 6]
Temporal score	16/16	2.5	1 - 4 [0- 6]
Occipital score	13/16	3.0	0 - 4 [0- 6]
Frontal score	16/16	2.0	2 - 3 [0- 6]
Left hemispheric score		5.5	3.7 - 7 [0-12]
Right hemispheric score		6.0	3.7 - 7 [0-12]
Basal Ganglia and Brain Stem score	6/16	0	0 - 3 [0-10]
Corpus Callosum score	13/16	1.0	0 - 3 [0- 3]
Global score		13.7	9.5 - 18 [0-40]

Notes: In parenthesis minimum-maximum score according to the semi-quantitative scale

As shown in Table 3, all children had white matter damage in parietal, temporal and frontal lobes, and 13 out of 16 also in the occipital lobe. However, lesions in the parietal white matter were more severe than in the other lobes (Wilcoxon z ranging from -3.2 to -3.6, $p<.001$). No differences emerged between left and right hemispheric scores.

Of the six children with basal ganglia and brainstem damage, four had an exclusive thalamic involvement, one had an exclusive involvement of the posterior limbs of internal capsule, one had both.

Of the 13 children with lesions of the corpus callosum (CC) all had an involvement of the posterior portion, eight of the middle portion and six had an involvement of the anterior portion.

Chi square analysis showed a significant association between thalamic and CC involvement, specifically between the thalamus and anterior ($\chi^2(1)=5.6$, $p<.05$) and middle CC ($\chi^2(1)=9.6$, $p<.005$).

The non-parametric bi-variate correlation analysis revealed negative relationships between the occipital lobar score and the Visuo-spatial Memory (rho(15)=-.65, $p<.005$) and Sensorimotor (rho(15)=-.59, $p<.01$) domain scores, as larger lesions were associated with lower performance. No other lobar score showed significant correlations with any NEPSY-II domain. This result was in part expected given the low variability of the lesions' extension in both the parietal and frontal lobes. A significant negative correlation was found between the CC score and the Visuo-spatial Memory (rho(15)=-.48, $p<.05$), Sensorimotor (rho(15)=-.50, $p<.05$) and Attention/Executive Functioning (rho(15)=-.51, $p<.05$) domains.

T-test analyses indicated that performance in the Attention/Executive Functioning domain was significantly worse in children with involvement of anterior ($t(14)=2.45$, $p<.05$) and middle ($t(14)=2.31$, $p<.05$) portions of the CC than in those without such involvement. No significant differences emerged at the other NEPSY-II domains in children with/without anterior or middle CC portion involvement. No comparative analysis was conducted on the posterior portion of CC because the majority of children showed abnormalities in this portion. Given that the analyses on the neuroanatomical findings revealed significant associations between the involvement of anterior and middle portions of the CC and thalamic abnormalities, children were grouped according to the presence (n=9) versus the absence (n=7) of damage in anterior or middle CC portions (anterior/middle) or in the thalamus. A significant difference was found in the Attention/Executive Functioning domain in the group with both CC and thalamic involvement with respect to the group without such abnormalities ($t(14)=2.35$, $p<.05$), while no differences emerged in the other NEPSY-II domains. The significant association between the presence of impairment in the Attention/Executive Functioning domain and both CC and thalamic damage was further supported by chi-square analysis ($\chi^2(1)=3.87$, $p<.05$). No significant differences emerged at the global score between children with presence/absence of impairment in the Attention/Executive Functioning domain. Figure 4 graphically represents the different lesion localization according to impaired or preserved Attention/Executive Functioning.

Figure 4

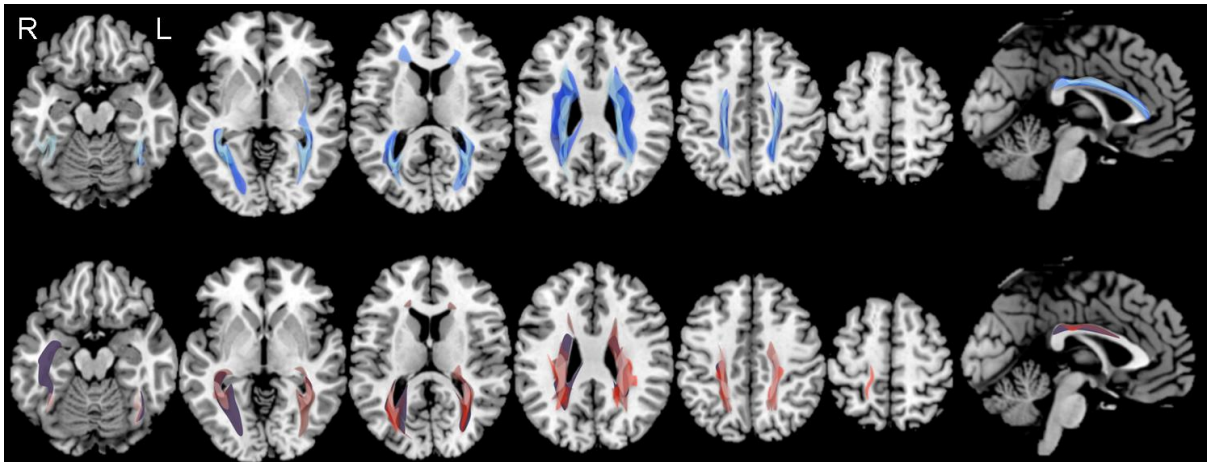

Figure 4: Representation of superimposed lesions collected by their graphical drawing in the template of the semi-quantitative scale, according to the presence (blue) or absence (red) of executive function impairment. Visual inspection of lesion representation reveals anterior involvement for the group with impaired executive functions (blue).

Discussion

This study is the first to describe the pattern of relative cognitive strengths and weaknesses in children with PVL using a comprehensive neuropsychological battery (NEPSY-II) and to correlate neuropsychological profiles with MRI findings assessed by a novel semi-quantitative classification system. In order to avoid bias due to variability in lesion type and clinical characterization, a homogeneous group of children with PVL and Verbal IQ>80 was selected. This approach can shed light on the understanding of the neuroanatomical underpinnings of the neuropsychological profile in children with bilateral CP and PVL, going beyond the known verbal-non-verbal IQ discrepancy and visuo-spatial core deficits. The central contribution of this study is that the neuropsychological impairment associated with PVL has a multilevel organization: visuo-spatial and sensorimotor abilities are common areas of impairment, while deficits in attention and inhibition work as additional weaknesses, specifically associated with damage to the anterior/middle corpus callosum or the thalamus.

A deficit in visuo-spatial processing was confirmed to be a neuropsychological marker of PVL, being present in 18 out of 20 children. The NEPSY-II, assessing visuo-perceptual abilities by several tests, allowed to better describe the widespread alteration of visuo-spatial skills both in perceptual and constructional tasks, a finding in agreement with the long standing literature on PVL (Koeda et al., 1992; Goto et al., 1994; Jacobson et al., 2000; Fazzi et al., 2004, Pagliano et al., 2007). The neurobiological models of visual functioning and its development underline the important role of two neural pathways of visual processing, the ventral and dorsal streams (Atkinson et al., 1999; Milner et al., 2008; Goodale et al., 2013; Klaver et al., 2015). Whereas the ventral pathways process visual input into perceptual representations integrating object characteristics and their spatial relations, the dorsal stream mediates spatial relations and visual control of actions. The widespread deficit found in children with PVL in the visuo-spatial domain suggests the simultaneous impairment of both visual streams (Fazzi et al., 2004; Korkman et al., 2007). Nevertheless, there were dissociations across components of visual processing: having to recall abstracts designs, children with PVL were more accurate in memorizing object form than position. This finding suggests, as previously found, that greater difficulties in spatial rather than form recognition are more typical of PVL (Fazzi et al., 2004).

Sensorimotor deficits were, in terms of frequency, second to visuo-spatial impairments, being present in 15 out of 20 children. The high prevalence of sensorimotor deficits was expected given the limitations in grasping, holding and manipulating objects in this population (Beckung et al., 2002; Eliasson et al., 2006). However, in the present study, impaired abilities were found in imitating hand positions and sequences, while finger tapping was preserved. This finding further suggests that the coordination of distal upper limb movements may be relatively preserved in

comparison to higher-order sensorimotor representation, integration and planning (Steenbergen et al., 2013).

The main finding of this study concerns the Attention/Executive Functioning domain, as it was impaired in a great number of PVL children (11/20), even in those subtests not requiring visuomotor processing such as Auditory Attention and Inhibition subtests. Deficits in attention and inhibition have been previously documented in children with bilateral CP (Pirila et al., 2004; Pirila et al., 2011; Korkman et al., 2008). The finding that Inhibition speed measures were impaired despite relatively preserved accuracy is new evidence suggesting specific difficulties in rapid information processing in children with PVL. Greater accuracy was found not only in the Inhibition subtests but also in non-timed categorical reasoning (Animal Sorting subtest) indicating that both are intact processes within the Attention/Executive Functioning domain. According to multicomponential models of executive functions (Miyake et al., 2000; Letho et al., 2003) these results suggest that PVL impacts on some sub-components of executive functioning but not all. Despite relatively preserved cognitive flexibility, slow inhibition and inefficient updating seem to be a core characteristic of many children with PVL.

In the Social Perception domain, eight out of 20 children were impaired, with lower performance with respect to Controls in the Theory of Mind than Affect recognition subtests. Although the literature is still scant, this finding supports previous findings by documenting, in PVL, a weakness in perception and understanding of others' intentions (Pavolva et al., 2012).

Finally, in the Verbal Memory and Language domains, children with PVL displayed normal performance, a finding that reflects the known profile of spared verbal intelligence (Pirila et al., 2004; Siguardottori et al., 2008; Korkman et al., 2008).

The neuropsychological results so far described underline the importance of using a comprehensive battery assessing many cognitive domains for analysing the profile of relative strengths and weaknesses, overcoming methodological constraints such as using tests with different standardization samples. By simultaneously "photographing" several neuropsychological skills in the same child, it was possible to highlight the crucial role played by executive dysfunction on several neuropsychological domains and on academic and social skills frequently found impaired in bilateral CP (Brovedani et al., 2014). In fact, deficits in attention and executive functioning significantly aggravated all other neuropsychological domains, from the most impaired skills, visuo-spatial abilities, to the most spared, such as language. One could speculate that attention and executive functioning impairment could selectively impact those skills requiring, more than others, inhibition and updating. In particular, the deficits in higher-order sensorimotor integration and motor planning may be in part attributed to reduced executive functions in terms of representation, planning and rapid integration of motor acts. Impaired executive functions were found in almost all

children with impaired performance in the Social perception domain. This finding is plausible as poor social abilities could be associated with inefficient executive functions hampering inhibition and switching of perspective taking. A deficit in a phonological processing task of the Language domain seems to be ascribed to an inefficient use of the active component of working memory. Performance was instead intact in a more passive memory task, such as nonsense-word repetition. It could also be speculated that an additional executive dysfunction may aggravate the frequent academic difficulties in children with CP, which have been reported, however, in only few studies (Downie et al., 2005; Pavolva et al., 2009; Jenks et al., 2009; Jenks et al., 2012; Van Rooijen et al., 2014).

To investigate the neurobiological underpinnings of cognitive performance in PVL, a detailed lesion analysis allowed correlating the severity of brain injury on structural MRI to the neuropsychological profiles. Large white matter lesions in the parietal lobe and posterior callosal thinning were present in all children and greater occipital damage was consistently associated with greater visuo-spatial and sensorimotor deficits. These findings confirm previous literature on the association between lesion extension in the posterior structures and visuo-spatial and sensorimotor impairment in PVL (Goto et al., 1994; Ito et al., 1996; Fazzi et al., 2004). That anterior/middle callosum involvement or thalamic abnormalities were associated with executive function impairment, in terms of inhibition speed deficit, is a new finding in PVL (for a review Weierink et al., 2013). The association between executive function and anterior callosum involvement has been documented in typical development with diffusion tensor imaging, demonstrating significant correlations between fractional anisotropy of frontal projections of the corpus callosum and inhibition performance at the NEPSY-II (Treit et al., 2014). In clinical populations (co-morbid ADHD and Developmental Coordination Disorder) fractional anisotropy values in the anterior/superior frontal of the corpus callosum correlated positively with performance at the Inhibition Switching subtest of the NEPSY-II (Langevin et al., 2015). In the same population of children, also cortical thickness in the right caudal middle frontal gyrus and left middle orbitofrontal gyrus correlated with NEPSY-II performance in this Attention/Executive Functioning domain subtest (Langevin et al., 2014). Moreover, in children with PVL, volumetric reduction of the thalamus was associated with working memory deficits with respect to preterms without lesion (Zubiaurre-Elorza et al., 2012).

In conclusion, this study brings a novel contribution to the literature by suggesting the presence of two possible PVL subgroups, diversified for lesion characteristics and specific neuropsychological profiles. A subgroup, with deficits in visuo-spatial and sensorimotor skills, was associated with PVL involving temporo-parieto-occipital white matter and posterior callosal portions. In the other PVL subgroup, with additional impairment in executive functions,

abnormalities involved also the anterior/middle callosal portions and the thalamus. In this second group, the executive functioning impairment, mainly involving selective attention and inhibition speed, also negatively affected visuo-spatial processing, sensorimotor integration and social perception.

The correlations found between lesion extension and neuropsychological profiles may have implications for tailoring interventions. Children with MRI abnormalities extending to anterior structures also showing executive function impairment could benefit from neuropsychological treatment focused on increasing inhibition and working memory skills, with positive cascade effects expected on other neuropsychological functions.

One limitation of the study lies in the relatively small sample size, although it must be underlined that the children group is homogeneous in terms of clinical and neuroradiological characteristics. This limitation implies that the results can be generalized to those children with PVL and normal verbal intelligence. Moreover, advanced neuroimaging techniques such as diffusion tractography could further increase the understanding of white matter pathology in CP and its relationship to function.

Study 2

Update on academic abilities in children with spastic cerebral palsy: differences across unilateral and bilateral clinical forms

Di Lieto MC, Chilosi A, Pecini C, Brovedani P, Cristofani P, Lenzi S, Fiori S, Cioni G. (in preparation)

Update on academic abilities in children with spastic cerebral palsy: differences across unilateral and bilateral clinical forms

Introduction

Cerebral Palsy (CP) is a group of permanent disorders of movement and posture occurring in the developing fetal or infant brain, and is often accompanied by disturbances of sensation, perception, cognition, communication, behaviour, by epilepsy and by secondary musculoskeletal problems (Rosenbaum et al., 2007). Seventy-percent of children with CP show disorders of higher cortical functioning (Liptak et al., 2004) and, consequently, are at high risk to develop academic difficulties. Although an investigation of the educational records of children with CP attending mainstream schools revealed that 46% of elementary school children had at least one specific academic impairment (Schenker et al., 2005), few and contradictory is the evidence academic achievements in children with CP.

The literature on the effects of congenital lesions on scholastic abilities has highlighted a trend towards poorer academic abilities in children with earlier lesions with respect to children with later occurring brain injury (Anderson et al., 2009). Several studies have described the crucial effects of other clinical factors on the neurocognitive outcome, such as epilepsy, cerebral visual impairment and premature birth (for a review see Brovedani and Cioni, 2014). The academic outcome also varies as a function of the clinical form of CP. Bilateral and unilateral CP are two clinical forms, indeed, different in terms of several clinical factors, such as timing of brain lesion, neuromotor disorders, visual impairment, premature birth and neuropsychological functioning.

The bilateral spastic CP is generally associated with preterm birth and is often, although not always, due to periventricular leukomalacia (PVL) occurring at the beginning of the third trimester of gestation. This lesion is the predominant neuropathological pattern underlying neurologic morbidity and may determine the disruption of several white matter pathways lying close to the lateral ventricles, e.g. the corticospinal tract, mostly resulting in spastic motor disorders, or the optic radiations, resulting in visual function deficits. General cognitive abilities are usually within low average-borderline range in children with bilateral CP with lower limbs more impaired than upper limbs, but a large discrepancy is consistently reported between Verbal and Performance Intelligence Quotients, with typically the latter being in the deficit range (Fedrizzi et al., 1993; Ito et al., 1996; Siguardardottir et al., 2008). According to lesion site or extension, several associative fibres may be disrupted, leading to neuropsychological deficits (Uggetti et al., 1996; Cioni et al., 2000; Fazzi et al., 2009; Guzzetta et al., 2010; Pavlova et al., 2013). Significant deficits in visuo-spatial skills have been extensively described in this clinical population (Koeda et al., 1992; Jacobson et al., 1998;

Lanzi et al., 1998; Pavlova et al., 2007; Pueyo et al., 2009; Fazzi et al., 2009; Jenks et al., 2012) and significant lower abilities in attention, inhibition and active components of memory have been also found (Schatz et al., 2001; Pirila et al., 2004; White et al., 2005; Korkman et al., 2008; Pueyo et al., 2009; Bottcher et al., 2009; Di Lieto et al., submitted).

The unilateral spastic CP is the most common expression of cerebral palsy (more than 38% of cases) and the second in terms of frequency, after bilateral CP, in premature infants (around 20% of cases) (Himmelmann et al., 2005; Cioni and Ferrarri, 2010). The brain lesions frequently found in unilateral CP are PVL, although the reported frequencies of PVL differ among studies (Cioni et al., 1999; Krageloh-Mann et al., 2007), brain malformations and cortical/subcortical lesions due to infarcts, mostly in the middle cerebral artery (Okumura et al., 1997; Yin et al., 2000; Nelson, 2002; Krageloh-Mann et al., 2007; Cioni et al., 2010). General intelligence is generally preserved (Chilosi et al., 2001; Ballantyne et al., 2007; Siguardardottir et al., 2008; Ricci et al., 2008; Westmacott et al., 2010; Riva et al., 2012) and cognitive profile is not associated with lesion side (Muter e coll., 1997; Ballantyne et al., 2008). However several clinical factors influence cognitive outcome, such as the timing of lesion, the lesion type (Ricci et al., 2008; Riva et al., 2012) and presence of epilepsy (Muter et al., 1997; Carlsson et al., 2003; Chilosi et al., 2001, 2005; Ballantyne et al., 2008). The timing of the lesion within this clinical form seems to be the main factor affecting inter- or intra-hemispheric language reorganization (Chilosi et al., 2001; 2005; Brizzolara et al., 2002; Liegeois et al., 2004; Chilosi et al., 2008; Guzzetta et al., 2008). The plasticity of brain networks may induce neuronal reorganization processes and thus affect cognitive functions, in particular speech and language functions (Aram, 1988; Thal et al. 1991; Trauner et al., 1993). Behavioural and neuroimaging studies of children with perinatal stroke in the left hemisphere suggest that the reorganization of language functions is a process which can last for a long time, based on the complexity of processes involved (Vicari et al., 2000; Chilosi et al., 2001; Chilosi et al.. 2008) including homologous areas in the right hemisphere or ipsilateral areas to the lesion (Staudt et al., 2001, 2002; Brizzolara, 2002; Liegeois, 2004; Guzzetta, 2008). The involvement of homologous areas in the right hemisphere due to the left hemisphere lesion, may produce a "crowding effect" of spatial functions that normally would have been mediated by these areas (Lidzba et al., 2006). The lesion type, instead, influence the neuropsychological profile in children with unilateral CP. Visuo-spatial deficits were found in children with brain lesion extended to optic radiation (Tinelli et al., 2013); difficulties in spatial processing of visual details and in perception of global configurations were reported in children with left hemisphere lesion (unilateral CP-LHL) and right hemisphere lesion (unilateral CP-RHL) respectively (Stiles et al., 2008). Impairment in problem-solving, planning and self-monitoring were found grater in children with unilateral CP-LHL with respect to unilateral CP-RHL (Kolk et al., 2002), while short- and long-term memory and language difficulties

were documented after lesions to either hemisphere, even if especially in the early years, deficit in oral comprehension and symbolic communication were more typical in children with unilateral CP-RHL and deficits in grammar and lexical productions in children with unilateral CP-LHL (Chilosi et al., 2001).

For both bilateral and unilateral CP, few and contradictory are the studies on scholastic abilities (Frampton et al., 1998; Downie et al., 2005; Ballantyne et al., 2008; Jenks et al., 2009). Frampton and co-workers (1998) investigated the prevalence of academic difficulties in children with unilateral CP, attending special or mainstream schools and found that 36% had at least one academic difficulty, 25% had difficulties in maths and 19% in reading decoding in particular. Jenks and co-workers (2009) found severe arithmetic difficulties in bilateral CP, and spelling and reading decoding difficulties were also reported, independent of extremely-low-birth weight status alone (Downie et al. 2005).

Given the few and relatively outdated studies focused on describing academic disorders in children with CP, the first aim of the present study was an update on the incidence of academic difficulties in a group of CP with preserved verbal or non-verbal intelligence. Reading decoding and comprehension were assessed in both bilateral and unilateral CP while arithmetic abilities in only bilateral CP, being frequently reported as impaired in the literature. The second aim was to document differences in academic achievement across the CP clinical forms, in an effort to understand how lesion and site of brain injury may influence academic performance.

Material and Methods

Participants

Forty-two children (24 females and 18 males) with spastic cerebral palsy, mean age 10.0 years (SD 2.8; range 6.3-16.1 years) and a mean gestational age at birth of 35 weeks (range 27-41 weeks) were selected from a larger sample of children with cerebral palsy referred in the years 2011-2014 to the Department of Developmental Neuroscience of Stella Maris Institute. Children were selected according to the following inclusion criteria: a) diagnosis of unilateral or bilateral cerebral palsy; b) absence of drug resistant epilepsy; c) absence of a psychiatric disorder diagnosis or sensory deficits that preclude testing; d) Verbal or Performance Intelligence Quotient >80, as assessed by WPPSI-III (Wechsler, 2002), WISC-III (Wechsler, 1992) or WISC-IV (Wechsler, 2003). Patients were divided into three clinical subgroups based on the type of cerebral palsy diagnosis: 16 children had unilateral CP, due to a left hemisphere lesion (unilateral CP-LHL), 12 children had left unilateral CP, due to a right hemisphere lesion (unilateral CP-RHL), and 14 children had bilateral CP, due to a bilateral lesion (bilateral CP).

The research project was approved by the Ethical Committee of Stella Maris Institute (n° 07/2012). Written consent was obtained from all participants' parents. All children were native Italian speakers.

Magnetic resonance imaging was classified by a child neuropsychiatrist with a strong neuroimaging background, who was blinded with respect to patients' neuropsychological findings. Brain lesions were classified according to the timing of lesion, preterm or periterm, and to the site of injury, cortical/subcortical and periventricular/subcortical lesions, related to different aetiopathogenesis, being due to infarcts mostly in the middle cerebral artery or to hypoxic-ischemic encephalopathy respectively. For 3 children scans were not available.

Academic abilities

The academic abilities were assessed by the reading decoding and comprehension tests and by arithmetic tests described below. The reading decoding and comprehension were assessed in all CP groups, while arithmetic abilities only in bilateral CP.

- Text reading: the child read a passage aloud within a 4-min time limit. Decoding speed was measured in seconds for syllable, while decoding accuracy in number of errors. Standardized data, expressed in z score, were calculated both for speed and accuracy (MT, Cornoldi and Colpo, 1995, 1998).
- Single words reading: the child read aloud lists of 112 words. Number of errors and speed of reading (seconds) were scored and converted to z scores according to standard reference data (DDE-2, Sartori et al., 2007).
- Text comprehension: after reading a story silently, the child had to answer 10 multiple-choice questions each with four alternatives. The number of correct response was computed and converted to z scores according to normative data (MT, Cornoldi and Colpo, 1995, 1998).
- Arithmetic abilities: the child was asked to performed different tasks: mental and written calculations, arithmetic facts, counting and transcribing digits. Both speed and accuracy were calculated for mental and writing calculations and for counting. The number of errors were considered for arithmetic facts and transcribing digits. Z scores were calculated according to standard data (AC-MT individual section, Cornoldi et al., 2002, 2003). This test was administered only in children with bilateral CP.

Statistical analysis

Performances was classified in three performance categories according to the normative standard scores: deficit (z score ≤ -1.5), borderline (-1.5< z score ≤-1) and average (z score > -1). Academic impairment was considered when performance on tests was either in the deficit or borderline range. For descriptive analysis, the reading decoding impairment was considered when at least one performance in word or text reading tests was impaired. The percentage of children with reading decoding or comprehension impairment was calculated in all the CP sample and considering the three CP subgroups separately. The percentage of arithmetic impairment was calculated only in the bilateral CP subgroup.

A paired t-test analysis was performed to compare verbal and non-verbal intelligence level within each CP subgroup. ANOVAs repetitive measure and Post-hoc comparisons (using LSD correction) were performed to identify differences in academic achievement in all CP sample and considering the CP subgroups separately. Only in the bilateral CP subgroup, ANOVAs and post-hoc comparisons was performed to analyze differences across the arithmetic tasks.

Bi-variate parametric correlations were conducted comparing academic performance and clinical characteristics (chronological age, gestational age and intelligence level) in all CP groups and in each CP subgroup separately. Chi-square analyses were performed to verify the associations between the presence/absence of impairment in reading decoding or comprehension and the timing (preterm and periterm) and the site (periventricular/subcortical and cortical/subcortical) of brain lesion.

Results

Clinical characteristics

The clinical characteristics of the sample are reported in Table 1. No subgroup differences were identified for gender and chronological age across the subgroups. The gestational ages were significantly lower in bilateral CP with respect to both unilateral CP-LHL and unilateral CP-RHL subgroups ($t(27)=3.8$; $p<.001$ and $t(23)=3.6$; $p<.005$ respectively). No differences between the unilateral CP subgroups at the gestational ages were found.

Table 1

Clinical characteristics of the sample

	Sex *male:female*	***Age*** *Mean(SD)*	***GA*** *Mean(SD)*	**Intelligence level**	
				Verbal *Mean (SD)*	**Non-verbal** *Mean (SD)*
Unilateral CP-LHL (n=16)	9:7	9.5(2.6)	37.1(1.0)	92.0(9.6)	92.8(3.2)
unilateral CP-RHL (n=12)	4:8	10.5(3.3)	37.0(1.1)	102.0(4.0)	89.9(3.1)
bilateral CP (n=14)	5:9	10.1(2.7)	31.8(0.9)	94.7(8.3)	76.1(4.2)
CP group (n=42)	18:24	10.0(2.8)	35.2(4.4)	95.8(11.1)	86.4(15.0)

At the Wechsler intelligence scales, the verbal intelligence level was significantly higher ($p<.05$) than non-verbal in 2 out of 16 children with unilateral CP-LHL, in 6 out of 12 children with unilateral CP-RHL and in 8 out of 14 children with bilateral CP. Within each CP subgroup, significant differences between verbal and non-verbal intelligence level were found both in unilateral CP-RHL ($t(11)=2.6$; $p<.05$) and in bilateral CP ($t(13)=4.9$; $p<.001$) in favour of the verbal intelligence level.

Academic impairment

Considering all the CP sample (n=42), the majority of children (23 out of 42, 55%) showed an academic impairment, intended as at least on one deficient or borderline performance in reading or comprehension tests. In particular, borderline or deficit performance were found in 21% (9/42) of children in reading decoding accuracy, in 26% (11/42) in reading decoding speed and in 26% (11/42) in reading comprehension. At the ANOVAs analysis no significant differences were found across reading decoding and comprehension performances ($F(1, 35)=1.14$, ns) in all the CP sample, nevertheless post-hoc comparisons revealed significant lower performance in the reading decoding speed in single word reading with respect to the reading decoding accuracy in text reading test ($t(38)=-2.47$, $p<.05$) and to the reading comprehension performance ($t(38)=-2.3$, $p<.05$) (see Figure 1).

Figure 1

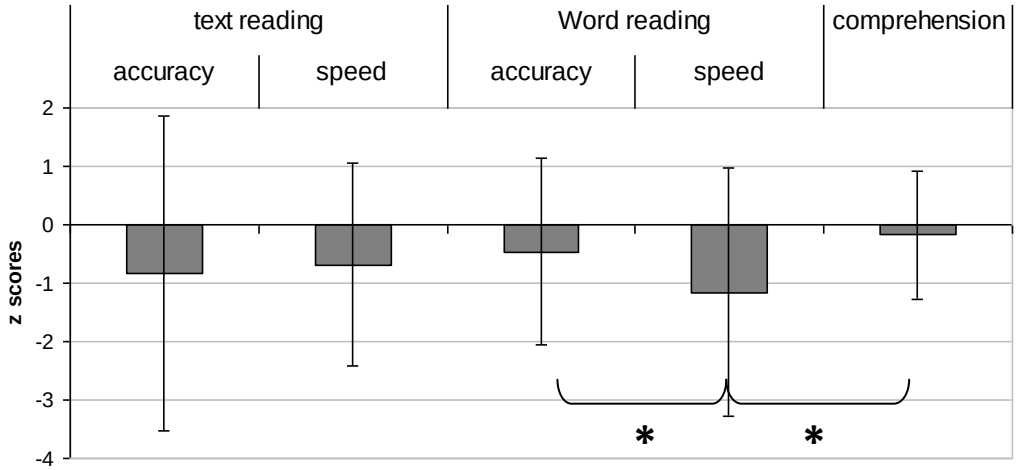

Figure 1: mean z scores for reading decoding and comprehension in the CP group. * significant differences (p<.05) at Post-hoc comparisons

Significant positive correlations were found between reading comprehension performances and the verbal intelligence level (r(42)=.39; <.01), and between the reading decoding speed in the word reading test and chronological age (r(38)=.40, p<.05). No other significant correlations were found in CP sample.

Intelligence level, academic performance and lesion characteristics of the single CP subgroups are reported in Table 2, 3 and 4. Concerning the different CP subgroups, academic impairment was found in 56% of children (9/16) with unilateral CP-LHL subgroup, in 41% (5/12) with unilateral CP-RHL and in 64% (9/14) with bilateral CP.

Table 2

Intelligence level, academic performance and lesion characteristics of children with unilateral CP-LHL

	Age *(y;m)*	Intelligence level		text reading test		word reading test		text comprehension test	lesion characteristics	
		Verbal	Non-verbal	accuracy	speed	accuracy	speed		site	timing
SL1	13;2	90	90	-1.69	-1.38	-2.00	-.85	.64	Periventricular/subcortical	periterm
SL2	7;1	90	80	-.31	.53	-.65	.28	-2.60	NA	NA
SL3	7;2	82	73	-.53	.18	.14	-1.11	.17	Cortical/subcortical	Periterm
SL4	7;1	81	121	-.74	.27	-.65	-.35	-1.56	NA	NA
SL5	8;1	90	103	.08	-.13	.14	-.05	-.61	Cortical/subcortical	periterm
SL6	10;2	95	90	-1.72	-2.56	-.67	-2.03	.24	Cortical/subcortical	preterm
SL7	7;0	96	97	.75	-.59	1.00	-2.00	-.29	Periventricular/subcortical	preterm
SL8	8;1	81	87	-.80	.01	.00	-1.10	-.91	Cortical/subcortical	periterm
SL9	9;0	79	87	-.85	-.33	.79	.08	-1.50	Periventricular/subcortical	preterm
SL10	11;1	100	111	-1.25	-.92	.	.	-1.60	Periventricular/subcortical	preterm
SL11	9;1	96	86	-1.66	-1.81	-1.67	-1.97	-.77	Cortical/subcortical	periterm
SL12	7;0	88	96	-.42	.30	.	.	1.48	Cortical/subcortical	periterm
SL13	8;1	118	98	-.27	-.73	.22	-1.09	.65	Periventricular/subcortical	preterm
SL14	15;0	99	102	-1.50	.90	-.19	-.12	.25	Cortical/subcortical	preterm
SL15	13;6	90	72	-.33	-.80	.33	.30	-.07	Cortical/subcortical	periterm
SL16	12;0	97	92	.35	.39	.50	.67	-1.03	Periventricular/subcortical	preterm

Table 3

Intelligence level, academic performances and lesion characteristics of children with unilateral CP-RHL

	Age *(y;m)*	Intelligence level		text reading test		word reading test		text comprehension test	lesion characteristics	
		Verbal	Non-verbal	accuracy	speed	accuracy	speed		site	timing
SR1	10;2	93	86	.85	.18	-.33	.51	.10	Cortical/subcortical	periterm
SR2	9;2	122	106	-.39	.03	-.33	-.80	.07	NA	NA
SR3	6;1	102	82	.64	.56	.66	.41	1.10	Cortical/subcortical	Periterm
SR4	11;5	87	94	.62	.19	.22	.15	-1.56	Periventricular/subcortical	Preterm
SR5	7;0	114	95	.49	-.87	-.19	-4.08	3.40	Periventricular/subcortical	Preterm
SR6	9;1	119	84	-.19	.26	-4.79	-1.68	.75	Cortical/subcortical	Periterm
SR7	6;1	92	95	-16.75	-7.87	-6.21	-5.33	-.77	Periventricular/subcortical	Preterm
SR8	10;1	81	76	.30	.20	-.43	-.36	-1.18	Periventricular/subcortical	Preterm
SR9	13;1	118	81	-.54	.26	.	.	.02	Periventricular/subcortical	Preterm
SR10	12;5	90	99	-.96	.27	-1.00	.23	-.64	Periventricular/subcortical	Periterm
SR11	15;1	103	75	-1.34	-.65	1.15	-.20	1.27	Periventricular/subcortical	Preterm
SR12	16;0	103	106	.12	-.31	.70	-.25	.77	Periventricular/subcortical	Periterm

Table 4

Intelligence level, academic performances and lesion characteristics of children with bilateral CP

	Age *(y;m)*	Intelligence level		text reading test		word reading test		text comprehension test	lesion characteristics	
		Verbal	Non-verbal	accuracy	speed	accuracy	speed		site	timing
SB1	8,5	103	59	.26	.22	1.00	.35	.14	Periventricular/subcortical	preterm
SB2	11,2	82	52	-.64	-4.32	.30	-6.80	1.14	Periventricular/subcortical	preterm
SB3	10,5	104	67	.97	-2.25	.66	-.29	-.24	Periventricular/subcortical	preterm
SB4	12,3	98	93	1.00	-.17	.33	-.62	-1.32	Periventricular/subcortical	preterm
SB5	9,1	88	54	-.85	.69	.66	-1.00	.07	Periventricular/subcortical	preterm
SB6	13,5	92	74	-.32	-.50	-1.00	-1.38	-1.37	Periventricular/subcortical	preterm
SB7	10,8	102	100	-.90	.10	.60	.40	-.14	Periventricular/subcortical	preterm
SB8	8,1	92	82	-1.06	-.13	.00	-1.63	-1.18	Periventricular/subcortical	preterm
SB9	15,9	82	87	-.04	.14	-.20	.80	.43	Periventricular/subcortical	preterm
SB10	9,7	99	89	-.35	-.15	1.00	.80	-1.60	Periventricular/subcortical	preterm
SB11	6,5	100	76	-.73	-1.07	-2.14	-4.33	.28	Periventricular/subcortical	preterm
SB12	6,3	100	89	.	.	-2.70	-3.70	.20	Periventricular/subcortical	preterm
SB13	.	102	85	.32	-.25	.25	1.12	.85	Periventricular/subcortical	preterm
SB14	8,8	82	58	-3.66	-5.90	-3.70	-8.40	-.15	Periventricular/subcortical	preterm

The percentages of children for each subtest with deficient or borderline performance in each reading decoding and comprehension tests is shown in Figure 2. In unilateral CP-LHL, 4 out of 16 children (25%) had borderline performance in reading comprehension, while a limited number of children (from 6% to 13%) showed borderline or deficient performance in reading decoding both in accuracy and speed. In unilateral CP-RHL, 2 out of 12 children (17%) were impaired in reading decoding both in speed and accuracy, while 2 out of 12 (17%) had borderline performance in reading comprehension. In bilateral CP, 4 out of 14 children (29%) had borderline performance in reading comprehension, and in the other 4 children (29%) reading decoding speed was in the deficit range. A limited number of children with bilateral CP (from 7% to 14%) showed borderline or deficit performance in reading decoding accuracy.

Figure 2

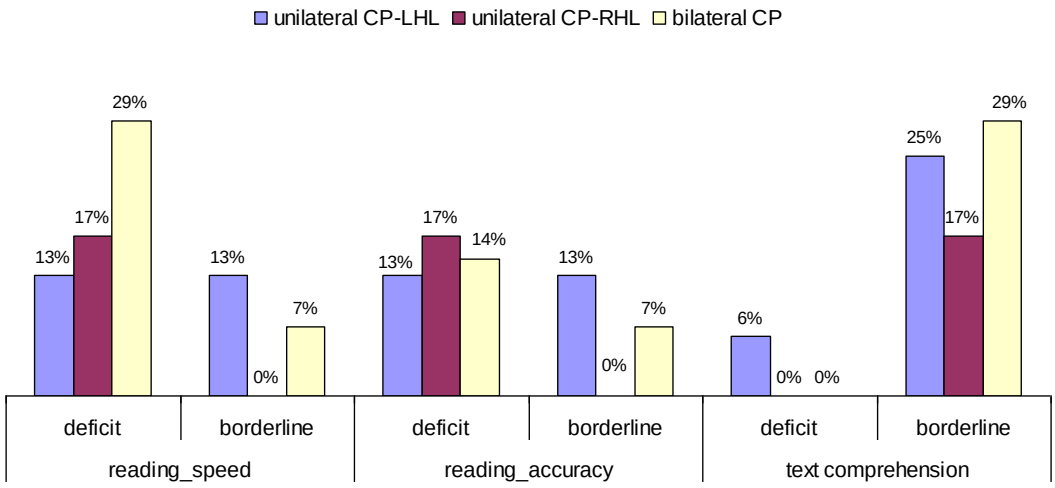

Figure 2: Percentage of children in each CP subgroup with deficit or borderline performance in reading decoding and comprehension tests

At the ANOVAs analyses no significant interaction across subgroups was found, comparing reading and comprehension tests ($F(2, 35)=.13$, ns).

A significant positive correlation was found between reading comprehension performance and verbal intelligence level in unilateral CP-RHL ($r(12)=.59$, $<.05$). No other significant correlations were found.

In the bilateral CP subgroup, impaired arithmetic abilities were found in 78% (11/14) of the children. In particular, the mental and written calculations were impaired in accuracy parameters in 36% and 31% respectively and in speed in 43% and 38% parameters respectively. Both the accuracy and speed in the counting task were relatively preserved in almost all children (only 18%

had impaired performance) while transcribing digits and arithmetic facts tasks were frequently impaired (31% and 43% respectively).

No significant differences at the ANOVAs analyses were found across arithmetic tasks ($F(1, 9)=1.32$, ns), nevertheless, post-hoc comparisons revealed significantly worse performance in arithmetic facts with respect to the speed in counting task ($t(10)=2.40$, $p<.05$) (see Figure 3).

Figure 3

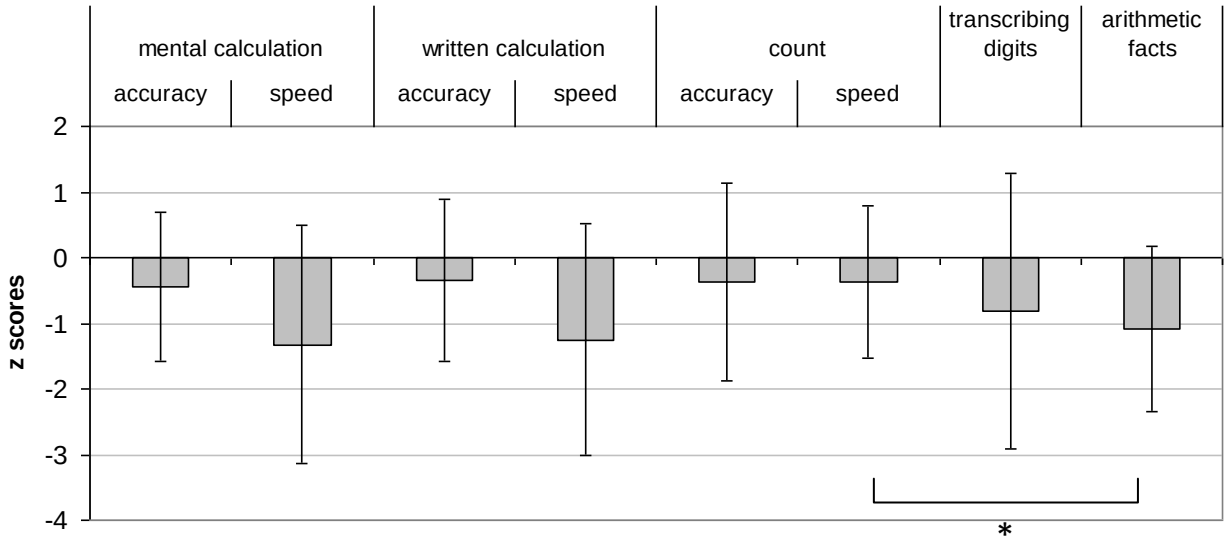

Figure 3: Mean z scores for each arithmetic task in bilateral CP. * significant differences ($p<.05$) at Post-hoc comparisons

Transcribing digits and arithmetic facts were positively correlated both with verbal ($r(13)=.72$, $<.005$ and $r(14)=.56$, $<.05$ respectively) and non-verbal intelligence level ($r(13)=.57$, $<.05$ and $r(14)=.63$, $<.05$ respectively). No other significant correlations were found in the bilateral CP subgroup.

The neuroanatomical classification according to the timing and site of brain lesions was applied to 39 brain MRIs, since for 3 brain MRIs visual inspection of the scans was not possible. The neuroanatomical characteristics of each CP subgroup are reported in Table 5. Within unilateral CP-LHL, 8 children showed cortical/subcortical lesions and 6 periventricular/subcortical lesions, in half of children (7/15) the injury occurred preterm and in the other half periterm (7/15). In unilateral CP-RHL, 3 children showed cortical/subcortical lesions and 8 periventricular/subcortical lesions, in

6 children the lesions occurred preterm and 5 periterm. In bilateral CP, as expected, all children showed periventricular/subcortical lesions that had occurred preterm.

Table 5

Number of children in each CP subgroup divided according to timing and site of brain lesion

	Site of brain lesion		***Timing of brain lesion***	
	Periventricular/ subcortical	*Cortical/ subcortical*	*Preterm*	*Periterm*
Unilateral CP-LHL (n=14)	6	8	7	7
unilateral CP-RHL (n=11)	8	3	6	5
bilateral CP (n=14)	14	0	14	0

The Chi-square analysis, performed only in unilateral subgroups for the lack of lesion variability in the bilateral CP subgroup, revealed significant associations between the presence/absence of impairment in reading comprehension performances and both timing ($\chi^2(1)=5.2$, $p<.05$) and site of brain lesion ($\chi^2(1)=4.6$, $p<.05$). A greater number of children with periventricular/subcortical and preterm brain lesion, indeed, showed impaired reading comprehension performance with respect to those children with cortical/subcortical and periterm brain lesion. No significant associations were found between lesion characteristics and reading decoding.

Discussion

The present study investigated the incidence of academic impairment in children with different clinical forms of CP, as unilateral and bilateral CP, in an effort to understand how timing and site of brain injury may influenced the academic performance in the presence of preserved verbal or non-verbal intelligence. Although several studies were aimed at describing the cognitive and neuropsychological profiles in children with unilateral and bilateral CP (Chilosi et al., 2011; Siguardardottir et al., 2008; Ballantyne et al., 2008; Fazzi et al., 2009; Riva et al., 2012; Pavlova et al., 2013, Di Lieto et al., submitted), few and contradictory are the findings on the impact of different congenital brain lesions on school competence. For this reason, the academic achievements were assessed and compared across three clinical CP forms, unilateral left or right and bilateral brain lesions. Moreover, in order to avoid bias due to intellectual disabilities, only children with preserved verbal or non-verbal intelligence level were selected.

The central contribution of the study is that the academic competence was impaired in a high percentage (55%) of children with CP, in words decoding speed in particular, and that this impairment varied in terms of frequency across the three CP clinical forms, even if not significantly. The neuroanatomical findings, moreover, documented the associations between academic competence and lesion characteristics, supporting the early vulnerability perspective (Anderson et al., 2009). Indeed, the academic impairment, in particular reading comprehension, was more frequently found in children with earlier lesions localized in periventricular/subcortical regions, with respect to those children with later occurring lesions localized in cortical/subcortical regions.

The percentage of children with CP and academic weaknesses and impairment (55%) was higher than the percentage documented in previous studies (Frampton et al., 1998; Schenker et al., 2005) mainly since, in the most of the studies, text reading comprehension assessment was not taken into consideration. Although the percentage of children with reading decoding impairment in this study (speed 26% and accuracy 21%) was similar to those found in the literature (Frampton et al., 1998), the present study found that a fourth of CP children presented text reading comprehension impairment revealing another important characteristics of the academic impairment profile in CP. Text comprehension, indeed, is seen as an end product of a number of subprocesses involving the mediation from visual input to phonological representation, in particular, and processes of language comprehension, in general, which in turn are modulated by working memory and attention (Witruk et al., 2002). The difficulties in efficiently integrating these cognitive subprocesses, subsumed by complex cortical networks, may be the basis of the text comprehension impairment in children with congenital brain lesions. The significant association between reading

comprehension performance and verbal intelligence level was also found, confirming previous literature on "poor comprehender" children (Nation, et al., 2004).

The significant discrepancy between speed and accuracy in the word reading test but not in text reading test, suggests the use of compensative strategies offered by semantic context in children with CP. Moreover, the strong relationship between speed word decoding and chronological age suggests the improvement in automatizing decoding with reading experience.

Different academic impairment profiles were found in the three CP subgroups investigated. In children with unilateral CP-LHL, the text reading comprehension was impaired in a high percentage of children (31%) while reading decoding difficulties were not so frequent (26%). Concerning the effects of pre- or periterm brain lesions on cerebral lateralization and specialization, neuropsychological studies have provided evidence that, in the case of left congenital lesions, the frequent reallocation of verbal functions to the right hemisphere may lead to a reorganization of the neural substrate and of cognitive functions. Atypical hemispheric lateralization for language, in terms of a shift of language processing to the right hemisphere, has been demonstrated by several studies that used the dichotic listening test (Carlsson et al., 1992; Isaacs et al., 1996; Brizzolara et al., 2002; Chilosi et al., 2005) and confirmed by functional MRI data (Staudt et al., 2001; Lidzba et al., 2006; Guzzetta et al., 2008). The neurofunctional reorganization of language processes in children with left hemisphere lesion may in part explain the frequent text reading comprehension impairment, a task with higher linguistic demands than reading decoding, such as semantic, grammar and lexical processes.

In children with unilateral CP-RHL, both reading decoding and comprehension impairments were infrequent (17%) and a significant correlation between verbal intelligence level and reading comprehension was also found. It's worth noting that these results may highlight a more efficient compensative role of verbal abilities on academic achievement in this CP subgroup with respect to the others.

In bilateral CP, reading comprehension and decoding speed were more impaired (29% for both) than reading decoding accuracy (from 7% to 14%) and the frequent arithmetic deficits (78%) confirmed previous studies (Jenks et al., 2009; Pavolva et al., 2009). The deficits in reading decoding and arithmetic abilities have been previously associated with the impairment in non-verbal intelligence level as well as to deficits in visuo-spatial, inhibition and updating, frequently described in this clinical population (Pirila et al., 2004; Fazzi et al., 2009; Jenks et al., 2012; Di Lieto et al., submitted). Selective spatial attention, visuo-perception abilities, processing of visual information and working memory, indeed, are crucial for reading decoding, as demonstrated in dyslexic children (Brannan et al., 1987; Facoetti et al., 2000, 2003), and for arithmetic abilities. Indeed, the low performance on arithmetic facts, found in the present study, may be related to the impairment in

updating and speed of processing because it requires quick recall of verbal information from memory.

Apart from these specific academic profiles, no significant differences were found across the three CP subgroups. These findings represent another important contribution because, if on the one hand they confirm the lack of reading differences between children with right and left hemisphere lesions (Ballantyne et al., 2008), on the other hand they specifically address the relationship between different reading decoding parameters (speed and accuracy), directly comparing children with unilateral and bilateral CP.

The correlations between behavioural reading phenotype and lesion characteristics indicate the importance of lesion timing and site in affecting academic achievements, supporting the early vulnerability perspective (Anderson et al., 2009). Anderson and co-workers, indeed, documented that children sustaining insult prior to or around the time of birth are most at risk for global deficits, while children with later insults escape relatively unscathed. Given these result, the present study brings a novel contribution in terms of the effects on academic achievement of lesions occurring within the perinatal period. The presence of preterm and periventricular/subcortical lesion, indeed, were significantly associated with impairment in text reading comprehension in unilateral brain lesions, confirming the early vulnerability perspective also in a narrower timing of brain insult.

In conclusion, these findings bring novel contributions on incidence of academic impairment in children with different congenital brain lesions at structural MRI documenting different frequencies of deficits in reading decoding and comprehension, even if not statistically significant. The higher incidence of academic impairment in children with CP (55%) and preserved verbal intelligence with respect to the general population (3%-4%, Consensus Conference, 2011), suggests that this clinical condition may be potentially at risk. Moreover, the presence of a preterm lesion in periventricular/subcortical regions was found more frequently associated to reading comprehension impairment with respect to perinatal and cortical/subcortical lesions, confirming and extending the early vulnerability perspective. Although further studies are necessary to confirm the impact of lesion characteristics and cognitive impairment on academic achievement, these results have important implications for the clinical assessment and for rehabilitative program also oriented to support learning of more efficient strategies to compensate academic difficulties in children with CP.

Study 3

CBCL profile in children with bilateral spastic cerebral palsy and preserved verbal intelligence: clinical and neuropsychological correlates

Di Lieto MC, Brovedani P, Pecini C, Dell'Omo M, Cioni G, Chilosi A. (in preparation)

CBCL profile in children with bilateral spastic cerebral palsy and preserved verbal intelligence: clinical and neuropsychological correlates

Introduction

Cerebral Palsy (CP) is defined as "a group of permanent disorders of movement and posture occurring in the developing fetal or infant brain" (Rosenbaum et al., 2007), also characterized by other clinical disturbances, as behaviour, cognition, communication, sensation, perception, by epilepsy and by secondary musculoskeletal problems. The prevalence of behavioural or emotional problems varies between 25% and 80% in children with CP, reflecting differences in age, severity of motor disorder, intellectual disabilities and level of parent distress (Hourcade et al., 1984; McDermott et al., 1996; Parkes et al., 2008, Siguardardottir et al., 2010; Romeo et al., 2010; Brossard-Racine et al., 2012). The psychopathological symptoms, indeed, were frequently associated with intellectual disability as only 15%-20% of children with CP and without intellectual disabilities showed behavioural and emotional problems (McDermott et al., 1996; Siguardardottir et al., 2010). Moreover, the psychopathological symptoms were also documented in children with preserved general cognitive abilities but with a wide discrepancy between verbal and non-verbal intelligence levels (Fuerst et al., 1990; Dorris et al., 2008; Assouline et al., 2012; Basten et al., 2014; Gregl et al., 2014).

The Child Behaviour Checklist (CBCL, Achenbach, 1991) is a standardized questionnaire that parents fill out to describe their children's behavioural and emotional problems. It is frequently used in different clinical population (Narzisi et al., 2013b; Georgsdottir et al., 2013; Carson et al., 2015; Masi et al., 2015) in order to investigate premorbid behavioural pattern. Child behavioural and emotional problems are rated both globally and along two main symptom dimensions, internalising (more typical in anxiety and depression) and externalising symptoms (such as aggressive or delinquent behaviour), with demonstrated reliability and validity in the literature (Cohen et al., 1985; Achenbach et al., 1991; Crijnen et al., 1999;).

Both externalizing and internalizing symptoms have been reported in children with CP: attention problems and social withdrawal have been described as the most problematic symptoms, aggressive behaviour and anxiety/depressed symptoms were also reported especially in pre-school ages (McDermott et al., 1996; Parkes et al., 2008; Siguardardottir et al., 2010). Some studies had tried to differentiate the behavioural and emotional problems across different clinical forms of CP, as unilateral and bilateral CP, finding externalizing symptoms more frequently in unilateral and internalizing symptoms more typical in bilateral CP (McDermott et al., 1996; Goodman et al., 1996; Romeo et al., 2010; Romeo et al., 2014).

Nevertheless, almost all studies on behavioural and emotional problems in CP included children with intellectual disabilities (McDermott et al., 1996; Siguardardottir et al., 2010; Romeo et al., 2014; Levy-Zaks et al., 2014), and none of them analyzed the association between behavioural and emotional problems and the neuropsychological profiles across CP clinical forms (Pueyo et al., 2009; Pavlova et al., 2013; Bodimeade et al., 2013; Piovesana et al., 2015; Gabis et al., 2015; Di Lieto et al., submitted). For this reason, the first aim of the present study was to describe behavioural and emotional characteristics in a group of children with bilateral cerebral palsy due to periventricular leukomalacia (PVL) with preserved verbal intelligence and homogeneous neuroradiological characteristics.

Bilateral spastic cerebral palsy is generally associated with preterm birth and is often, although not always, due to PVL, a white matter lesion surrounding the lateral ventricles of the brain. In this clinical condition, general cognitive abilities are usually within low average-borderline range, but a large discrepancy is consistently reported between Verbal and Performance Intelligence Quotients (IQ), with only the latter being in the deficit range (Fedrizzi et al., 1993; Ito et al., 1996; Yokochi et al., 2000; Sigurdardottir et al., 2008; Fazzi et al., 2009; Pavlova et al., 2009; Pavlova et al., 2013). The neuropsychological profile is characterized by deficits in visuo-spatial skills and significant lower abilities in attention, inhibition and active components of memory (Koeda et al., 1992; Jacobson et al., 1998; Lanzi et al., 1998; Schatz et al., 2001; Pirila et al., 2004; White et al., 2005; Pavlova et al., 2007; Korkman et al., 2008; Pueyo et al., 2009; Bottcher et al., 2009; Fazzi et al., 2009; Jenks et al., 2012; Di Lieto et al., submitted).

Given the clinical characteristics, preterm birth and gross motor impairment, and the specific neuropsychological profile of children with bilateral cerebral palsy due to PVL, the second aim of the study was to analyze the relationship between the behavioural and emotional problems and both the clinical and neuropsychological profile.

Material and Methods

Participants

Twenty children (11 females and 9 males) with bilateral spastic cerebral palsy due to PVL (mean age 8;7 years, SD 3;0, range 4;9-15;9 years) and a mean gestational age at birth of 31 weeks (range 28-41) were selected from a larger sample of children with cerebral palsy referred in the years 2013-2014 to the Department of Developmental Neuroscience of Stella Maris Institute. Children were selected according to the following inclusion criteria: a) neuroradiological diagnosis of PVL documented at brain MRI performed after age 2 years; b) levels I to III at the Manual Ability Classification System (MACS, Eliasson et al., 2006); c) absence of drug-resistant epilepsy; d) absence of a psychiatric disorder diagnosis or sensory deficits that preclude testing; e) Verbal

Intelligence Quotient >80, as assessed in the last year prior to recruitment by WPPSI-III (Wechsler, 2002), WISC-III (Wechsler, 1992) or WISC-IV (Wechsler, 2003). The research was approved by the Ethical Committee of Stella Maris Institute (n° 07/2012). Written consent was obtained from all participants' parents who also gave informed consent to publication of results. All children were native Italian speakers.

Study variable

Motor and visual assessment

The Gross Motor Classification System (GMCS) (Palisano et al., 1997) was used to determine gross motor skills. Children were classified according to five motor levels: walk without restriction (level I); walk without assistive devices but limitation in walking outdoors (level II); walk with assistive mobility devices (level III); self-mobility with limitations (level IV); self-mobility severely limited even with use of assistive technology (level V).

Visual functions were assessed for the presence of deficits in the following areas: stereopsis, ocular motility, visual field and acuity. Visual functions were classified as no deficit, mildly impaired (maximum two deficits), and severely impaired (three or more deficits).

Behavioural and emotional characteristics

The Child Behavioural Checklist (CBCL, Achenbach et al., 2000; Italian adaptation by Frigerio et al., 1998) is the most widely used parent report checklist that measures a broad range of behavioral and emotional problems. Two versions according to the age range of children are available: The CBCL/6-18 is appropriate for children within the age range of 6-18 years and the CBCL/1½-5 is designed for children aged 1½ to 5 years. The CBCL includes several item behavioural scales (118 for CBCL/6-18 and 113 item for CBCL/1½-5) and the parent is asked to rate the frequency of each behaviour on a three-point Likert scale (0, not true; 1, somewhat or sometimes true; 2, very true or often true). The CBCL includes eight main syndrome subscales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behaviour, Aggressive Behaviour) and of six DSM-oriented subscales (Achenbach et al., 2001: Affective Disorder, Anxiety Disorder, Somatic Problem, Attention deficit/Hyperactivity problem, Oppositional Defiant Problem, Conduct Problems). Three syndrome composite scales are available: Internalizing scale (sum of Anxious/Depressed, Withdrawn/Depressed and Somatic Complaints), Externalizing scale (sum of Aggressive Behaviour and Rule Breaking Behaviour in CBCL/6-18 version, or Aggressive Behaviour and Attention Problems in CBCL/1½-5 version) and Total Problem scale (sum of all syndrome subscales). For the syndrome subscales, T scores less than 67 are considered in the

normal range, T scores ranging from 67-70 are considered in the borderline range, and T scores above 70 are in the clinical range. For Total Problems, Externalizing Problems, and Internalizing Problems, T scores less than 60 are considered in the normal range, 60-63 represent borderline range scores, and scores greater than 63 are in the clinical range (Achenbach, 1991 and 2001).

Neuropsychological Assessment

Neuropsychological functioning was assessed with the NEPSY-II, a comprehensive neuropsychological battery developed for the evaluation of children aged 3 to 16 years (Korkman et al., 2007; Italian adaptation by Urgesi et al., 2011). Only the NEPSY-II domains found impaired in the literature (Pirila et al., 2004; Korkman et al., 2008; Di Lieto et al., submitted) were administered: Attention/Executive Functioning, Social Perception, Sensorimotor, and Visuo-spatial Processing. For the mean domain score only the subtests expressed in scaled scores (mean 10; SD 3) according to normative data (Urgesi et al., 2011) were considered.

The Attention/Executive Functioning domain included:

- Visual Attention subtest, to evaluate visual search requiring crossing out one or two targets amongst a variable number of distractor stimuli;
- Inhibition subtest, to evaluate the ability to inhibit automatic responses in favour of novel responses and to switch between response types. A composite score was obtained including both accuracy and speed.

The Sensorimotor domain included:

- Finger Tapping subtest, to evaluate the ability to imitate a series of finger movements (single and sequences) with the dominant and non-dominant hand. Speed is recorded;
- Imitating Hand Positions subtest, to evaluate visuo-motor planning requiring to imitate finger positions;
- Visuomotor Precision subtest, to evaluate visuo-motor integration by requiring to draw a line following paths of different widths and spatial complexity. A composite score which included both accuracy and speed is measured;
- Manual Motor Sequences subtest, to evaluate visuo-motor planning by requiring imitation of a series of hand movements.

The Social Perception domain included:

- Theory of Mind subtest, to evaluate the capacity to predict reactions or behaviours in certain situations. Verbal or pictorial descriptions of several social situations are presented and questions asked that require an understanding of the characters' point of view;

- Affect Recognition subtest, to evaluate the ability to recognize emotional expressions by matching two children's faces expressing the same emotions among three or more alternatives.

The Visuo-spatial Processing domain included:

- Design Copying subtest, to evaluate visuo-motor integration by requiring to copy geometric figures of increasing complexity;
- Block Construction subtest, to evaluate constructional praxis by requiring production of the three-dimensional constructions of increasing complexity starting from either a three- or a two-dimensional model;
- Geometric Puzzles subtest, evaluates mental rotation by requiring to recognize rotated geometric shapes among a series of distractors.

Statistical analyses

Raw scores of CBCL scales and subscales were converted to age-standardized scores (T scores having a mean = 50 and SD = 10) based on the normative samples of children within the same age range (Achenbach, 1991).

Raw scores for each NEPSY-II subtest, were expressed as scaled scores (mean 10; SD 3) with respect to the age-matched normative sample values (Urgesi et al., 2011). Four mean domain scores were calculated by averaging the scaled scores of all subtests included in each domain.

T-test were used to compare Externalizing and Internalizing syndrome scales. Repeated measure ANOVA and Post-hoc comparisons were performed to verify the differences across the eight syndrome subscales and across the six DSM-oriented subscales (Bonferroni's correction).

Bi-variate non-parametric correlations were used to correlate CBCL syndrome scales and subscales with clinical characteristics (intelligence levels, levels of gross motor impairment and gestational ages) and neuropsychological profile (NEPSY-II mean domain scores).

Results

Behavioural and emotional characteristics of bilateral CP with PVL

Nineteen CBCL/6-18 and 1 CBCL/1½-5 were considered for analysis.

At the Internalizing syndrome scale, 40% of children (8/20) had scores in the borderline or clinical range: 35% (7/20) showed clinical and 5% (1/20) borderline range scores. At the Externalizing syndrome scale, no clinical range score was found, while only 15% of children (3/20) obtained borderline scores. At the Total Problem syndrome scale, 10% (2/20) showed clinical and 25% (5/20) borderline range scores. As shown in Figure 1, the difference between Internalizing and

Externalizing syndrome scales was significant (t(19)=2.33, p<.05). No statistical differences between males and females were found in any of the CBCL scales (p>.05).

Figure 1

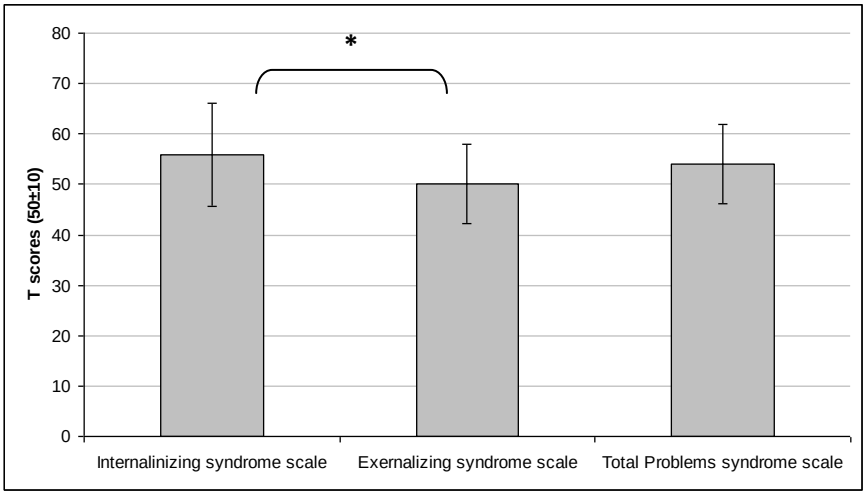

Figure 1: Mean and SD of T scores in each CBCL syndrome scale

At the CBCL syndrome subscales, significant differences across the eight syndrome subscales were found (F(7, 126)=4.07, p<.05). Post-hoc comparisons revealed that the Withdrawn/Depressed and the Social Problems subscales had significantly higher scores than the Aggressive Behaviour subscale (t(18)=5,26, p<.05; t(18)=5,71, p<.05 respectively). Scores in the clinical range were found in 10% (2/20) of children in the Withdrawn/Depressed subscale and in 15% in the Social Problems subscale. No children showed scores in the clinical range in the Aggressive Behaviour subscale.

At the DSM-oriented subscales, significant differences were found at the repeated measure ANOVA (F(5, 90)=4.01, p<.05). Post-hoc comparisons revealed that the Affective Problem subscale had a significantly higher score than the Oppositional Defiant Problems (t(18)=4.47, p<.05) and the Conduct Problems (t(18)=5.16, p<.05) subscales. None of the children had scores either in clinical or borderline range in any of the DSM-oriented subscales.

Clinical correlates of the CBCL profile

Motor, visual and cognitive functions are reported in Table 1. At motor functioning assessment (GMFCS), 2 children were classified at Level I, 10 at Level II, 5 at Level III and 3 at Level IV. Sixteen out of 18 children showed mildly impaired and 2 out 18 normal visual functions (visual functions were not available for two children). At the Wechsler intelligence scales, verbal

indices were significantly higher than non-verbal ($t(19)=6.1$, $p<.001$). T scores for each child at the Internalizing and Externalizing scales are shown in Table 1

Table 1

Clinical characteristics of the sample

	Sex	Age y; m	GA	Motor Functions GMFCS level	Visual Functions	Intelligence		CBCL composite scales		
						Verbal*	Non-Verbal*	Intern.	Extern.	Total Problem
S1	F	4;10	29	III	NA	106	76	58	51	54
S2	F	8;05	32	III	Mild	102	100	50	44	45
S3	M	6;03	28	II	NA	88	93	48	50	51
S4	M	6;11	32	I	Mild	100	76	41	46	47
S5	F	7;02	32	II	Mild	82	58	66	61	69
S6	M	9;11	29	IV	Mild	88	54	65	58	60
S7	M	8;08	30	II	Mild	100	82	65	46	60
S8	F	6;05	32	II	Normal	100	80	54	34	45
S9	M	7;10	32	II	Mild	100	62	63	48	53
S10	F	5;10	31	II	Normal	104	87	59	56	57
S11	M	5;10	31	III	Mild	108	82	34	58	53
S12	F	6;05	32	IV	Mild	100	89	62	60	60
S13	M	15;10	41	II	Mild	92	82	40	43	38
S14	F	9;05	28	III	Mild	99	89	64	51	60
S15	F	10;09	32	I	Mild	82	87	56	37	48
S16	F	13;09	29	IV	Mild	92	74	74	50	62
S17	M	10;03	30	II	Mild	103	59	65	62	64
S18	F	9;06	34	II	Mild	82	52	52	57	59
S19	M	8;09	28	III	Mild	102	85	52	48	47
S20	F	12;03	34	II	Mild	98	93	51	43	49

Note: GA, gestational age; GMFCS, Gross-Motor Function Classification System; NA, Not Available; Verbal, Verbal IQ (WISC-III, WPPSI-III) or Verbal Comprehension Index (WISC-IV); Non-verbal*, Performance IQ (WPPSI-III) or Perceptual Organization Index (WISC-III) or Perceptual Reasoning Index (WISC-IV)*

As shown in Figure 2, the bi-variate non-parametrical correlations between CBCL syndrome scales and clinical characteristics of the sample (intelligence indices, levels of gross motor impairment and gestational ages) revealed significant negative correlations between both the Internalized and the Total Problems scales and the non-verbal intelligence index ($rho(20)=-.46$, $p<.05$; $rho(20)=-.47$, $p<.05$ respectively). Thus low non-verbal intelligence was associated with higher scores in Internalizing or Total Problems scales.

Figure 2

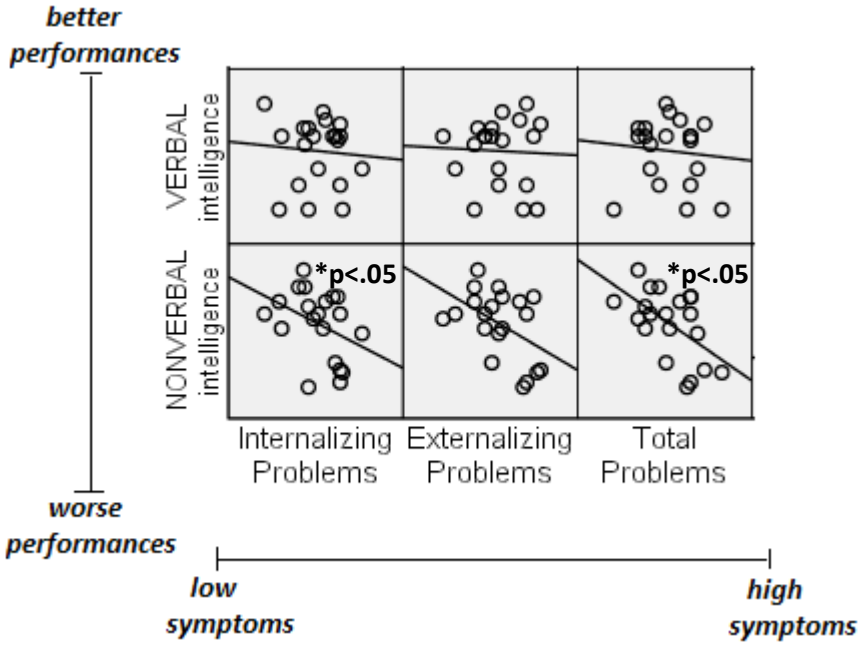

Figure 2: The matrix scatter show the bi-variate correlations between verbal and non-verbal intelligence and the CBCL composite syndrome scales

The bi-variate non-parametrical correlations between CBCL subscales and clinical characteristics revealed significant negative correlations between non-verbal intelligence index and Withdrawn/Depressed subscale (rho(20)=-.51, p<.05) and Attention problem subscale (rho(20)=-.45, p<.05). A negative significant correlation was also found between verbal intelligence index and Somatic Complaints subscale (rho(20)=-.45, p<.05).

Negative correlations were also found between non-verbal intelligence index and DSM-oriented subscales, such as the Somatic Problem (rho(20)=-.47, p<.05), the Attention deficit/Hyperactivity Problem (rho(20)=-.50, p<.01) and the Oppositional Defiant Problem (rho(20)=-46, p<.05) subscales.

Neuropsychological functioning correlates of the CBCL profile

For the purpose of the study, performance in each NEPSY-II domain was classified into 3 categories according to the normative standard scores: deficit (scaled scores 1 to 3), borderline (4 to 6) and average (>7). The distribution of impaired performance, comprising deficient or borderline functioning, revealed that the great majority of children were impaired in Visuo-spatial Processing and Sensorimotor domains (65% in both domains). Many children were also impaired in the Attention/Executive Functioning (50%) and Social Perception (40%) domains.

As shown Figure 3, the non-parametric bi-variate correlations revealed significant negative correlations between the Internalizing syndrome scale and Sensorimotor domain (rho(20)=-.47, p<.05). No other significant correlation was found between NEPSY-II domains and CBCL composite scales.

Figure 3

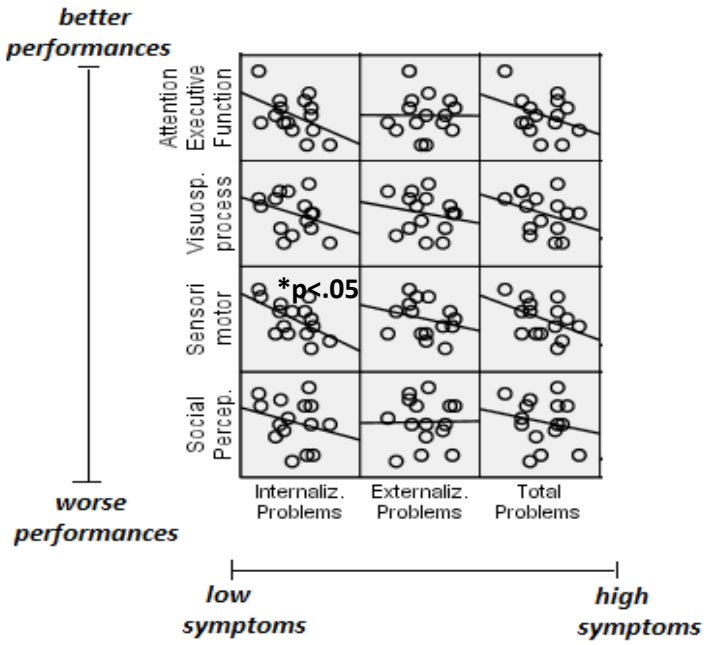

Figure 3: The matrix scatter shows the bi-variate correlations between NEPSY-II domains and the CBCL composite syndrome scales

The bi-variate correlations between the CBCL subscales and NEPSY-II domain or subtests highlighted that the Withdraw/Depressed and Somatic Complaints subscales were negatively correlated with both Visuo-spatial Processing (rho(20)=-.52, p<.05 and rho(20)=-.45, p<.05 respectively) and Sensorimotor (rho(20)=-.62, p<.005 and rho(20)=-.56, p<.01 respectively) domains. The Withdrawn/Depressed subscale was also negatively correlated with the Social Perception domain (rho(15)=-.61, p<.05).

Within the Visuo-spatial domain, the Somatic Complaints and Somatic Problems subscales were significantly correlated with the Block construction subtest (rho(20)=-.57, p<.01 and rho(19)=-.59, p<.01 respectively). The Oppositional Defiant Problems subscale was negatively correlated with the Puzzle photos subtest (rho(12)=-.58, p<.05).

Discussion

The study is the first to specify the relationship between behavioural and emotional problems and both clinical and neuropsychological profile in a group of children with bilateral cerebral palsy due to PVL, preserved verbal intelligence and homogeneous brain lesion.

Internalizing problems were confirmed to be a frequent emotional and behavioural characteristic of children with PVL (40%), concerning withdrawn behaviour, social and somatic problems in particular. Previous studies described greater internalizing problems in this clinical form of CP with respect to the other forms, such as unilateral CP where externalizing problems were more typical (Goodman et al., 1996; Romeo et al., 2010). In particular Romeo and co-workers found a comparable percentage of internalizing problems in children with bilateral cerebral palsy (diplegia 41%).

The central contribution of the study is that, even without a psychiatric diagnosis, children with PVL show internalizing problems, especially concerning social withdrawal and somatic preoccupations, strongly associated with non-verbal intelligence, visuo-spatial and manual abilities as well as social competences but not with executive functioning.

The present study confirmed and further specified the association between psychopathological symptoms profile and intelligence level found in the literature. Previous researches documented, in pre-school and pre-adolescent children, a greater risk of developing both internalizing and externalizing symptoms in children with a non verbal intelligence deficit, and externalizing symptoms in children with verbal intelligence deficit (Anderson et al., 1989; Dietz et al., 1997). In the present study non-verbal intelligence was strongly associated with internalizing symptoms, characterised by withdrawn/depressed and somatic problems, while level of verbal intelligence correlated with somatic complaints. This finding suggests the crucial role of non-verbal impairment, concerning visual perception, visual organization and visual construction skills, on the development of social problems and the protective effect of preserved linguistic and verbal competences on somatic symptoms.

A second main finding of the study concerned the neuropsychological correlates of the emotional and behavioural characteristics of children with PVL. Manual-motor and visuo-spatial abilities were frequently impaired in PVL (60% and 70% respectively), as found previously in the literature (Koeda et al., 1992; Jacobson et al., 1998; Lanzi et al., 1998; Pavlova et al., 2007; Pueyo et al., 2009; Fazzi et al., 2009; Jenks et al., 2012; Steenbergen et al., 2013; Di Lieto et al., submitted), and were significantly correlated with internalizing problems. The Social Perception domain, impaired in 40% of children, was also related to internalizing symptoms, while no association was found between executive functioning, impaired in the half of the sample, and any behavioural and emotional characteristics.

The association between internalizing problems and the degree of manual-motor impairment was found both in simple coordination and in higher-order sensorimotor representation, such as manual planning, imitation hand position and finger or manual sequences. Although less is known about the relationship between psychopathological symptoms pattern and motor disorders, previous studies on children with poor motor abilities, such as developmental coordination disorder and minor neurological dysfunction, also reported internalizing problems due to social isolation from peers (Green et al. 2006; Tseng et al., 2007; Cairney et al., 2010 and 2011; Peters et al. 2014). Longitudinal studies confirmed these findings, documenting the predictive role of both early motor skills and childhood motor skills on anxious/depressive symptoms in childhood and adolescence (Sigurdsson et al., 2002; Piek et al., 2010).

The significant correlations between visuo-constructional competences and internalizing symptoms, somatic complaints and withdrawal in particular, was a new finding. This relationship suggests a bi-directional association between visuo-spatial abilities and internalizing symptoms in PVL: the difficulties to see an object as a set of parts and consequently to re-construct it from its parts, may have an effect on social self-concept and self-ideas, but at the same time the anxious and withdrawn behaviours may overstate the visuo-constructional deficit.

The internalizing problems were also significantly associated with social difficulties, in particular in the interpretation of other people's action and intentions (theory of mind), confirming that the ability to regulate behaviours and emotions depends in part on the ability to flexibly monitor one's own progress toward a goal (Henderson et al., 2015). The relationship between social difficulties and internalizing symptoms was previously documented also in other pediatric populations, such as inflammatory bowel disease (Greenley et al., 2010), glycogen storage disease type 1 (Storch et al., 2008) and in spina bifida (Essner, 2014), suggesting that motor limitations hampering social interactions, reducing self-esteem related to peer, increasing anxiety in social situations may explain the internalizing symptoms.

The absence of a relationship between psychopathological symptoms pattern and executive functioning in children with PVL, was another new finding. The literature was not yet found a convergence on the role of executive function on internalizing problems. Some authors, indeed, have suggested that inflexibility and rigidity have a significant effect on withdrawn behaviours (Ghassabian et al., 2014) while others have asserted that internalizing behaviour could be attributed to a consistently enhanced ability to inhibit responses, even in cases where this is not appropriate (Quay, 1988; Koijmans et al., 2000).

In conclusion, this study brings a novel contribution by specifying emotional and behavioural characteristic of children with bilateral cerebral palsy due to PVL by suggesting possible neuropsychological correlates. The internalizing problems, social withdrawal and somatic

problems in particular, characterized a high percentage of children with PVL, even if none of the children had a psychiatric diagnosis. Moreover, the internalizing problems were strongly correlated with the degree of impairment in non-verbal intelligence, manual-motor abilities, visuo-spatial abilities as well as social competences. Although further studies with a larger samples are necessary, these findings contribute to enhance knowledge on the neuropsychological and clinical factors which can have a potential effect on the psychopathological development in children with PVL, that should be taken into consideration when planning both assessment and treatment.

Study 4

Adaptive Working Memory training intervention in children with bilateral cerebral palsy due to PVL: A neuropsychological study

Di Lieto M.C., Pecini C., Brovedani P., Dell'Omo M., Chilosi A., Cioni G. (in preparation)

Adaptive Working Memory training intervention in children with bilateral cerebral palsy due to PVL: A neuropsychological study

Introduction

Working memory (WM) is considered the ability to retain and manipulate information for brief periods of time. It is important in several complex cognitive functions, such as academic learning, planning and organizing daily life activities. School-based activities, indeed, such as math and reading, depend on the student's ability to pay attention to several instructions or information and to hold and integrate them (Adams et al., 1997; Gathercole et al., 2008; Oberauer et al., 2008; Jenks et al, 2009; Diamond et al., 2011; Diamond et al., 2012; Wass et al., 2015). Working memory belongs to the family of top-down mental processes, called executive functions (Miyake et al., 2000; Lehto et al., 2003). Miyake and co-workers (2000), identified three moderately correlated factors within the executive functions domain: 'Shifting', the ability to switch between multiple tasks, mental sets or response rules; 'Inhibition', the cognitive ability to suppress dominant responses in favour of goal-appropriate responses; 'Updating', the ability to actively manipulate relevant information in WM rather than passively store information. Recent reviews of executive function interventions underlined that WM and attentional control must be continually challenged and may be considered as "tools for learning", favouring the acquisition of skills in other cognitive domains (Diamond et al., 2011; Spencer-Smith et al., 2015; Wass et al., 2012, 2015).

CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden) is an evidence-based and intensive tele-rehabilitation program, comprising a number of visuo-spatial and verbal exercises that automatically change the level of difficulty, depending on the individual child's performance. Recent neurofunctional and behavioural studies reported a CogMed Working Memory Training effect in different clinical conditions, such as ADHD (Klingberg et al., 2005; Beck et al., 2010; Gibson et al., 2011; Chacko et al., 2013), acquired brain injury (Lundqvist et al., 2010) and preterm birth (Løhaugen et al., 2010; Grunewald et al., 2013). Functional MRI studies on healthy adults showed increase BOLD activity in parietal and prefrontal regions at the end of CogMed training (Olesen et al., 2004; McNab et al., 2009; Brehmer et al., 2011), suggesting a training-induced plasticity in the neural systems underlining WM abilities. Behavioural findings, moreover, documented a positive generalization effect of CogMed Working Memory Training on other cognitive abilities, such as reasoning

(Klingberg et al., 2005; Jaeggi et al., 2008), sustained attention (Westerberg et al., 2007; Thorell et al., 2009; Lundqvist et al., 2010), inhibition, task switching (Thorell et al., 2009; Lundqvist et al., 2010) and academic abilities (Klingberg et al., 2005; Holmes et al., 2009 and 2010; Loosli et al., 2012).

No study so far has explored the effects of a WM training after periventricular white matter lesions in premature children a clinical population known to be at risk of developing executive function deficits as revealed by a number of studies (Schatz et al., 2001; Pirila et al., 2004; White et al., 2005; Korkman et al., 2008; Jenks et al., 2009; Bottcher et al., 2009; Pirila et al., 2011; Di Lieto et al., submitted).

Periventricular leukomalacia (PVL) is a brain lesion that may determine the disruption of several white matter pathways lying close to the lateral ventricles, as the corticospinal tract, mostly resulting in spastic motor disorders, such as bilateral cerebral palsy, or the optic radiations, resulting in visual function deficits. According to lesion extension, from the periventricular layer to the middle white matter, several associative fibres may be disrupted, leading to neuropsychological deficits (Uggetti et al., 1996; Cioni et al., 2000; Fazzi et al., 2009; Guzzetta et al., 2010; Pavlova et al., 2013). Children with PVL have generally spared verbal abilities, as measured by verbal IQ tests, while non-verbal intelligence and especially visuo-perceptual and visuo-spatial abilities are consistently impaired (Fedrizzi et al., 1993; Ito et al., 1996; Yokochi et al., 2000; Sigurdardottir et al., 2008; Fazzi et al., 2009; Pavlova et al., 2009; Pavlova et al., 2013). Beyond visuo-spatial deficits and impaired non-verbal intelligence, weak executive functions have been found in children with PVL, especially in terms of working memory and inhibition (Schatz et al., 2001; Pirila et al., 2004; White et al., 2005; Korkman et al., 2008; Jenks et al., 2009; Bottcher et al., 2009; Pirila et al., 2011; Di Lieto et al., submitted).

In spite of the great number of interventions on cerebral palsy especially oriented on body motor structures and functions (eg., botulinum toxic inoculation, fitness training, diazepam treatment) or activities (eg. bimanual training, goal-directed training, home program for motor activities performance), generalization of treatment to academic or daily life abilities has been rarely documented (for a review Novak et al., 2013). In addition to motor physical training, only recently have the interventions on cerebral palsy been focused also on psychological well-being and social participation (Butler et al., 2001; Pennington et al., 2004; Blauw-Hospers et al., 2007; Tuerseley-Dixon et al., 2010) and on cognitive improvement (Blauw-Hospers et al., 2007; Ziviani et al., 2010). Only one ongoing research is focused on improving executive functions in children with cerebral palsy with a working memory training (Løhaugen et al., 2014). In prematurity, a

clinical condition strongly associated with an increase risk to develop cerebral palsy (Trønnes et al., 2014), three non-randomised and one ongoing control trial studies have been published with CogMed training. Benefits of the training have been found in trained and un-trained memory tasks in these studies, especially in visual and verbal memory, auditory attention and phonological awareness (Løhaugen et al., 2011; Grunewaldt et al., 2013; Pascoe et al., 2013).

Given the neuropsychological impairment profile of children with PVL, characterized by executive function and attentional impairment, the aims of this study were to specifically train a weak neuropsychological function, working memory, and to verify if such training improves other neuropsychological functions as visuo-spatial and sensorimotor abilities defined as core deficits in the literature. This study, moreover, offers a contribution on the effect of a home-based training in a clinical condition, cerebral palsy, subjected to frequent to hospitalizations for treatment and assessment. The study has been registered with ClinicalTrials.gov, numbers NCT02342990, on January 20, 2015.

Methods

Participants

Sample size was calculated by expected effect size method (Kadam et al., 2010). Based on a previous pilot study in our Institute and on findings by Lundqvist and collaborators (2010), the effect size estimates on the primary outcome described below was .60 for which a sample size of 20 children was required.

Twenty children (11 females, 9 males) with PVL (mean age 7;2 years, SD: 2;4 range: 4;1 – 13;1 years) and a mean gestational age at birth of 31 weeks (range: 28-37) were selected from a larger sample of children with cerebral palsy referred in the years 2014-2015 to the Department of Developmental Neuroscience of IRCCS Stella Maris Institute. Children were selected according to the following inclusion criteria: neuroradiological diagnosis of PVL documented at brain MRI performed after age 2 years (by images or on neuroradiological reports); level I to III at the Manual Ability Classification System (MACS- Eliasson et al., 2006); absence of drug-resistant epilepsy; absence of a psychiatric disorder diagnosis or sensory deficits that precludes testing; Verbal Intelligence Quotient above 80, as assessed by WPPSI-III (Wechsler, 2002), WISC-III (Wechsler, 1992) or WISC-IV (Wechsler, 2003) in the year prior to recruitment. All children were native Italian speakers and followed standard motor rehabilitation.

The research project was approved by the Ethical Committee of IRCCS Stella Maris Institute (n° 13/2013). Written consent was obtained from all participants' parents who also gave informed consent to publication of results.

Motor and Visual assessment

The Gross Motor Classification System (GMCS) (Palisano et al., 1997) was used to determine gross motor skills. Children were classified in five motor levels: walk without restriction (level I); walk without assistive devices but limitation in walking outdoors (level II); walk with assistive mobility devices (level III); self-mobility with limitations (level IV); self-mobility is severely limited even with use of assistive technology (level V).

Visual functions were assessed for the presence of the following visual deficits: stereopsis impairment, deficits in ocular motility, visual field or visual acuity. Children were classified as follows: normal, absence of deficits; mildly impaired, one or two visual deficits; severely impaired, three or more deficits.

Procedure

Intervention program

CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden) is an home-based software to improve WM by computer games that increase progressively increase WM demands. CogMed training contains a variety of computerized, game-format tasks that are adaptive; the level of difficulty is adjusted automatically to the WM span of the child on each task. This training is available in three on-line versions depending on the child's age. Almost all children included in the study used the school age version (CogMed RM), while three of them (S3, S8 and S17 in Table 1) used the pre-school version (CogMed JM). The CogMed RM includes 12 visuo-spatial and verbal tasks, eight tasks are provided for each training session for 45 minutes a day; the CogMed JM consists of 7 visuo-spatial and verbal tasks for 20 minutes a day. A training period of five weeks, for a total of 25 sessions, was performed by each child at home. A certified coach introduced CogMed program to the child and his/her family, establishing with them reward systems, goals and treatment planning and followed the training progress weekly calling the families to give advice based on the uploaded results. After the training, two type of final CogMed indices were automatically provided by the program: CogMed improvement index, a measures of working memory improvement, and CogMed progress

indicators, which assessed visuo-spatial and verbal WM span from two tests adapted from the Odd One Out of the Automated Working Memory Assessment (AWMA; Alloway, 2007). For a detailed description of CogMed Working Memory Training see www.cogmed.com/program.

Study Design

As shown in Figure 1, a Stepped Wedge randomized trial design (Brown et al., 2006) was chosen to randomly split the children into two groups (Cluster A, n=10 and Cluster B, n=10), for sequential rollout of the training. There was no difference in chronological age, sex and gestational age between the two Clusters. Both Clusters were assessed with neuropsychological tests at time point T0. Then children in Cluster B started immediately CogMed training, while those in Cluster A did not receive any training in the same period, continuing their daily life activities as usual. Six/seven weeks later, all children (Cluster A and B) were retested (time point T1). Then Cluster A started CogMed training and six/seven weeks later was retested at time point T2.

Training effect was evaluated comparing pre- and post- training performances in all children (both Cluster A and Cluster B), while test-re-test effect was calculated comparing performances at T0 and T1 time points only in Cluster A.

Figure 1

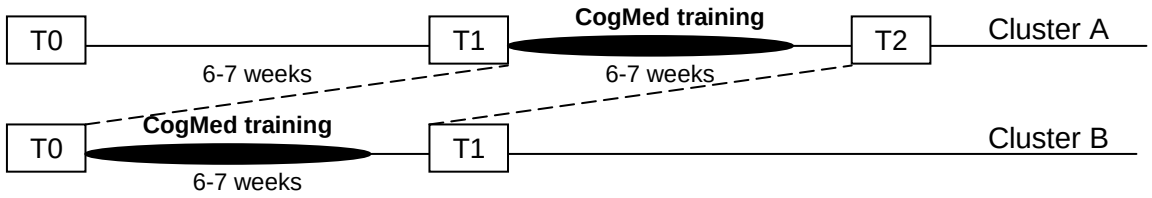

Figure 1: The study population was divided in two groups, called Cluster A and Cluster B. The figure illustrates the time points of the stepped wedge randomized trial design

Outcome measures

The primary outcome measure was the CogMed Improvement index provided by the program and calculated subtracting the Start Index (the mean of the three best successful trials on days 2 and 3) from the Max Index (the mean of the three best successful trials on the two best training days). A CogMed Improvement Index grater than 14 (>1 SD) represented a significant improvement of WM abilities.

The CogMed progress indicators assessed visuo-spatial and verbal WM span with two tests, Working Memory and Following Instructions, presented by the program at the beginning, the middle and the end of the training. The Working Memory test was an exercise where the child had to identify the different shape from a set of three and remember its location; in the Following Instruction test the child listened to a set of instructions and then clicked on or dragged objects seen on the screen in a specific order. Both tests scores were expressed in span scores.

The CogMed rating scale questionnaire was filled out by the parents for monitoring the child's behaviour before and after the training period. The questionnaire collected quantitative data, expressed as raw scores on changes in the child's behaviour in the followings areas: inattention, hyperactivity and impulsivity. This questionnaire was filled only by parents of school-aged children, as provided by CogMed.

The following neuropsychological areas were assessed: executive function and attention, manual planning, visuo-spatial memory and visuo-spatial processing. Four mean scaled scores for each neuropsychological area were calculated by the subtests expressed in scaled scores (mean 10; SD 3). For subtests analysis, all the following subtests were considered and expressed as raw scores.

The executive functions and attention area was assessed by some subtests, included in the Executive Function/Attention and Language domains of the NEPSY-II (Korkman et al., 2007). All the following subtests concurred to the Executive function and attention mean score, except Auditory Attention and Response Set subtest:

- Visual Attention subtest, evaluating visual search requiring crossing out one or two targets amongst a variable number of distractor stimuli;

- Auditory Attention and Response Set subtest, evaluating sustained auditory attention and the ability to shift and update new and complex set of rules involving the inhibition of previously learned responses;

- Inhibition subtest, evaluating the ability to inhibit automatic responses in favour of novel responses and to switch between response types. It is divided into three conditions: naming, inhibition and switching. Both accuracy (number of errors) and speed are obtained for each condition;

- Phonological processing subtest, evaluating phonemic awareness by requiring to identify pictures corresponding to given word segments and to create new words by omitting or substituting a syllable or a phoneme.

Manual planning was tested by all subtests included in the Sensorimotor domain at the NEPSY-II. All the following subtests contributed to the Manual planning mean score:

- Fingertip Tapping subtest, evaluating the ability to imitate a series of finger movements (single and sequences) with the dominant and non-dominant hand. Speed is recorded;

- Imitating Hand Positions subtest evaluating visuo-motor planning requiring to imitate finger positions;

- Visuo-motor Precision subtest, evaluating visuo-motor integration by requiring to draw a line following paths of different widths and spatial complexity. Both accuracy (number of errors) and speed are measured;

- Manual Motor Sequences subtest, evaluating visuo-motor planning by requiring imitation of a series of hand movements.

Visuo-spatial memory was measured by the Memory for Design subtest included in the Memory and Learning domain at the NEPSY-II. This subtest evaluates visuo-spatial memory by requiring to identify form and position of an abstract design on a grid with 4 to 10 distractors. Content (visual form recognition) and spatial (localization) scores are obtained. Memory for Design Delayed is administered 15 to 25 minutes later.

Visuo-spatial processing was evaluated by all subtest included in Visuo-spatial processing domain at the NEPSY-II. All the following subtests concurred to the Visuo-spatial elaboration mean score, except Route Finding and Arrows subtests:

- Design Copying subtest, evaluating visuo-motor integration by requiring to copy geometric figures of increasing complexity;

- Block Construction subtest, evaluating constructional praxis by requiring production of the three-dimensional constructions of increasing complexity starting from either a three- or a two-dimensional model;

- Geometric Puzzles subtest, evaluating mental rotation by requiring to recognize rotated geometric shapes among a series of distractors;

Statistical analysis

Statistical Package for Social Sciences, version 13.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) was used for statistical analyses.

Both parametric and non-parametric analyses were used because dependent variables were measured both with continuous and ordinal scales.

A first set of analysis, using Mann-Withney and Student's t tests, were conducted to verify the absence of clinical and performance differences at pre-training assessment between Cluster A and Cluster B.

The presence of pre- and post- training differences at the primary outcome measure were analyzed by Wilcoxon Signer Rank and Student's t tests.

Two-factors repeated measures ANOVAs and post-hoc comparisons were calculated, with the four neuropsychological areas (Executive functions and attention, Visuo-spatial processing, Manual Planning and Visuo-spatial Memory) and test-retest (baseline and pre-training assessment) or training effects (pre- and post-training assessment) as within subjects factors. Cohen's d was calculated to determine the effect size of pre- and post- training performances for each neuropsychological area and subtest by G*Power program (Faul et al., 2007).

Non-parametric bi-variate correlations between clinical characteristics (intelligence level, chronological age, gestational age and GMFCS and CogMed Improvement index or the degree of improvement for each neuropsychological area and subtest) were performed.

Results

Clinical characteristics of the sample

Motor, visual and cognitive functions of the study population reported in Table 1.

Table 1

Clinical characteristics of PVL children

	Sex	***GA***	***Age*** *(y;m)*	***Motor Functions*** GMFCS Level	***Visual Functions deficits***	***Intelligence*** Verbal*	***Intelligence*** Non-Verbal*
Cluster A							
S1	M	28	9;0	III	Mild	102	85
S2	M	28	6;0	II	NA	88	93
S3	F	29	4;1	III	NA	106	76
S4	M	31	5;1	III	Mild	108	82
S5	F	29	5;1	IV	Mild	114	104
S6	F	29	7;0	II	Mild	94	95
S7	M	35	6;1	III	No	92	61
S8	F	30	5;1	II	No	100	82
S9	F	32	8;0	II	Mild	82	58
S10	M	*30*	*8;7*	II	Mild	*112*	*82*
Mean (SD)	**-**	***30.1(2.1)***	***6;7(1;7)***	**-**	**-**	***99.8(10.6)***	***81.8(14.3)***
Cluster B							
S11	M	31	8;1	II	Mild	104	87
S12	F	32	9;1	III	Mild	102	100
S13	F	32	6;1	IV	Mild	100	89
S14	M	30	11;0	II	Mild	103	59
S15	F	32	6;0	II	No	100	80
S16	F	34	13;1	II	Mild	98	93
S17	F	32	4;1	II	Mild	112	91
S18	M	37	6;0	I	Mild	124	111
S19	M	32	7;8	II	Mild	100	62
S20	F	28	9;7	III	Mild	99	89
Mean (SD)	**-**	***32.0(2.3)***	***7;8(2;9)***	**- -**	**-**	***104.2(8.0)***	***86.1(15.8)***

Note: GA, gestational age; GMFCS, Gross-Motor Function Classification System; NA, Not Available; verbal, Verbal IQ (WISC-III, WPPSI-III) or Verbal Comprehension Index (WISC-IV); non verbal*, Performance IQ(WPPSI-III) or Perceptual Organization Index (WISC-III) or Perceptual Reasoning Index (WISC-IV).*

At gross motor functioning assessment (GMFCS), 1 child walked without restriction (Level I), 11 children had limitations in walking but did not use assistive devices (Level II), 6 walked with assistive devices (Level III) and 2 showed self-mobility with limitation (Level IV). Visual functions were mildly impaired in the majority of children (15/20) while 3 did not show visual impairment.

As expected from the literature, almost all children (18 out of 20) had verbal intelligence greater the non-verbal. Between Cluster A and Cluster B, no significant differences were found in verbal and non-verbal indices ($t(18)=-.85$, ns; $t(18)=-.23$, ns; respectively) and in GMFCS (Mann-Whitney $Z=-.97$, ns). No differences between two Clusters were found in Start CogMed index ($t(16)=-1.16$; ns) and in any other neuropsychological area at pre-training assessment. At subtest level analysis, Cluster B had a significantly greater performance in Design Copy subtest than Cluster A. No other differences were found between Clusters.

Training effects on the CogMed indices

Two children, included in Cluster A, did not complete the training due to family problems and their performance was only used to verify practice test-retest effects. All the other children (n=18) completed the 25-day training period and were tested at all scheduled time points.

As shown in Table 2, the Max Index was significantly higher than the Start Index ($t(17)=-7.85$, $p<.001$) and a large effect size was found ($d=1.26$). The Improvement Index, indeed, was higher than the improvement cut-off value (mean 25.2; SD 13.53; range between 8-52; cut off >14). The Improvement Index did not correlate with the Start max index ($r(18)=.37$, ns).

Table 2

CogMed working Memory indices

	Start Index	Max Index	Improvement Index
S1	64	83	19*
S2	73	125	52*
S3	33	41	8
S4	48	63	16*
S5	54	76	22*
S6	42	78	35*
S8	39	54	14*
S9	67	80	14*
S11	61	77	16*
S12	77	101	24*
S13	66	79	12
S14	69	95	26*
S15	55	89	34*
S16	78	128	49*
S17	45	67	22*
S18	64	88	24*
S19	36	52	16*
S20	51	101	50*
Mean (SD)	*56.8(14.1)*	*82.0(23.0)*	*25.2(13.5)*

* significant improvement (≥1 SD from mean)

The span scores in the Following Instruction test significantly improved at the end session with respect to both the beginning ($Z=-2.9$; $p<.005$) and the middle ($Z=-2.5$, $p<.01$) sessions. The span scores in the Working Memory test and the behavioural profile at the parent rating scales did not significantly change after the training.

Training effect on neuropsychological measures

Within Cluster A, tested twice before training, no test-retest ($F(1, 9)=1.44$; ns) or interactions with neuropsychological areas ($F(3, 27)=0.54$; ns) were found. At the subtest level, a test-retest effect was found in inhibition accuracy ($t(8)=5.7$, $p<.05$), finger tapping ($t(7)=3.1$, $p<.05$) and manual motor sequences ($t(9)=-2.6$, $p<.05$). Thus, in order to avoid test-retest bias, the standard scores of these subtests were not used to calculate the mean score for the neuropsychological area in the following analysis.

Pre- and post- training neuropsychological performances in both Clusters A and B showed a general improvement as there was a significant training effect ($F(1, 15)=13.56$; $p<.005$) without interaction across areas ($F(3, 45)=0.81$; ns). Explorations of single subject data (Table 3), showed a higher number of children with improvement performance in the Visuo-spatial processing and Executive functions and attention areas (moderate effect size) than in the Manual Planning and Visuo-spatial Memory areas.

Table 3

Comparison between pre-and post-training performance
at the neuropsychological areas

Neuropsychological area	***Pre-training Mean(SD) n=18***	***Post-training Mean(SD) n=18***	***Effect size d***	***Children with improvement***
Executive function and attention	*8.0 (2.4)*	*8.9 (2.3)*	*0.3*	***13/18***
Manual planning	*5.0 (2.4)*	*5.2 (2.3)*	*0.1*	***10/16***
Visuo-spatial Memory	*7.3 (2.3)*	*8.4 (3.3)*	*0.5^*	***8/18***
Visuo-spatial Processing	*6.4 (2.0)*	*7.4 (2.1)*	*0.5^*	***14/18***

Note: ^moderate effect size (Cohen's d > |.5|)

The differences between pre- and post- training performances for each subtest are reported in Table 4. Within Executive function and attention area, the speed in inhibition and naming conditions in Inhibition subtests were significantly reduced with a moderate effect size for the former in post- training assessment with respect to pre-training assessment. Phonological Processing also significantly improved.

In the Visuo-spatial Memory area, better performance at the end of the training was found in Memory of Design (immediate content condition) subtest with a moderate effect size.

In the Manual Planning area, no subtests resulted significantly improved.

Within the Visuo-spatial processing area, significantly improved performance was found in Block Construction, Geometric Puzzle and Route Finding subtests with large effect sizes for the first and moderate for the others.

Table 4

Comparison between pre- and post- training performances at the single subtest

Outcome		***Pre-training*** *Mean (SD)*	***Post-training*** *Mean (SD)*	***t***	***df***	***p***	***Cohen's d***	***Children with improv.***
Executive function and attention	*Visual Attention*	*4.6(11.9)*	*7.4(12.3)*	*-2.0*	*16*	*.057*	*0.2*	*13/18*
	Auditory Attention	*23.4(6.9)*	*25.8(4.5)*	*-1.9*	*14*	*.083*	*0.4*	*7/15*
	Response Set	*27.2(9.0)*	*30.4(6.4)*	*-1.5*	*7*	*.182*	*0.4*	*4/8*
	Speed in naming	*99.9(37.6)*	*92.2(41.3)*	*2.1*	*15*	*.050**	*0.2*	*11/16*
	Accuracy in naming	*3.9(3.0)*	*2.9(2.7)*	*1.6*	*15*	*.119*	*0.3*	*9/16*
	Speed in inhibition	*154.4(40.5)*	*136.2(57.2)*	*2.9*	*15*	*.011**	*0.4*	*12/16*
	Speed in switching	*151.7(73.1)*	*132.7(46.8)*	*1.6*	*8*	*.151*	*0.3*	*6/9*
	Accuracy in switching	*15.1(16.1)*	*12.3(15.0)*	*1.3*	*8*	*.224*	*0.2*	*6/9*
	Phonological processing	*32.4(11.2)*	*34.1(12.0)*	*-2.8*	*15*	*.013**	*0.1*	*10/16*
Visuo-spatial Memory	*Immediate content*	*37.9(11.8)*	*42.2(11.6)*	*-2.3*	*17*	*.036**	*0.4*	*13/18*
	Immediate spatial	*17.1(7.7)*	*18.8(9.0)*	*-1.5*	*17*	*.139*	*0.2*	*9/18*
	Delay content	*11.4(4.0)*	*12.4(4.8)*	*-1.3*	*15*	*.213*	*0.2*	*10/16*
	Delay spatial	*5.9(2.0)*	*6.5(2.8)*	*-1.1*	*15*	*.270*	*0.2*	*9/16*
Manual planning	*Imitation hand position*	*10.3(4.4)*	*11.4(4.2)*	*-1.7*	*15*	*.101*	*0.2*	*11/16*
	Speed in Visuomotor	*106.1(43.0)*	*126.0(64.9)*	*-1.5*	*14*	*.164*	*0.3*	*4/15*
	Accuracy in Visuomotor	*60.1(48.1)*	*53.7(50.3)*	*.6*	*14*	*.558*	*0.1*	*9/15*
Visuo-spatial Elaboration	*Design Copy*	*7.4(3.2)*	*7.8(3.3)*	*-1.2*	*16*	*.248*	*0.1*	*9/17*
	Block construction	*8.1(2.4)*	*9.9(2.2)*	*-5.0*	*15*	*.001**	*0.8^*	*14/16*
	Geometric Puzzle	*17.1(6.5)*	*19.8(6.0)*	*-3.5*	*16*	*.003**	*0.4*	*12/17*
	Route Finding	*3.1(3.2)*	*4.8(3.3)*	*-2.9*	*13*	*.013**	*0.5*	*10/14*
	Arrows	*13.8(9.4)*	*15.5(6.9)*	*-1.3*	*14*	*.225*	*0.2*	*9/15*

*Significance after Bonferroni's Correction ($p < .05$); ^large effect size (Cohen's d > |.8|)

Correlations between training effects and clinical profile

No significant correlations between verbal or non-verbal intelligence and CogMed Improvement index were found (rho(18)=-.31, ns; t(18)=.46, ns; respectively). Chronological age was significantly correlated with Start and Max indices (rho(18)=.60, <.01; rho(18)=.67, <.01 respectively), but not with Improvement index. No correlations were found between other clinical characteristics and CogMed indices.

A significant negative correlation was found between chronological age and the degree of improvement in Visuo-spatial processing area (rho(18)=-.60,<.01), thus younger PVL children improved more in visuo-spatial skills than older children. Non-verbal intelligence was positively correlated with the degree of improvement in the Auditory Attention subtest (rho(15)=-61, <.05). Verbal intelligence level was negatively correlated with the response time in the Inhibition subtest (rho(16)=-.61, <.05) and positively correlated with Memory of Design (immediate content condition) subtest (rho(18)=.48, <.05). The level of GMFCS was significantly positively correlated with the improvement in the Imitation hand position subtest (rho(16)=.62, <.01), thus children with severe gross motor impairment had a higher degree of improvement in manual planning with respect to those with mild gross motor impairment. Children were grouped according to the degree of impairment at the GMFCS: 11 children were mildly impaired (level I and II), while 7 were severely impaired (level III and IV). The two groups did not show differences in Start index at pre-training assessment, while children with severe gross motor impairment displayed significant greater improvements in the Imitation hand position subtest (t(14)=-2.68; p<.05) and those with mild gross motor impairment showed better improvement in Block Construction subtests (t(14)=2.32; p<.05). No other significant differences were found between the two PVL subgroups.

Discussion

This study is the first aimed at improving neuropsychological functioning by a home-based working memory training in children with cerebral palsy and PVL. The rationale of the study stemmed from the lack of evidence of specific cognitive training in the presence of executive function impairments, especially in working memory, after congenital bilateral white matter lesions. More evidence is available on the effects of cognitive training on psychological wellness in children with cerebral palsy and bilateral lesions (Novack et al., 2013).

The main finding of the study was that working memory training was efficient in improving both trained working memory abilities and other non-trained neuropsychological functions, such as visuo-spatial processing, inhibition and verbal updating in children with PVL.

The strengths of the study were the implementation of an evidence-based training, CogMed (Klingberg et al., 2005) and of a comprehensive neuropsychological assessment to document possible generalization to the other cognitive areas found impaired in PVL such as visuo-spatial, manual planning and executive functions (Pirila et al., 2004; Korkman et al., 2008; Fazzi et al., 2009; Pavlova et al., 2009; Pirila et al., 2011; Pavlova et al., 2013; Di Lieto et al., submitted). Another strength was the inclusion of a group of children homogeneous in terms of brain lesion and clinical characteristics.

In agreement with previous studies in different clinical populations, the direct effect of the training on working memory abilities was demonstrated in PVL by the significant and large improvement in CogMed indices (Klingberg et al., 2002; Beck et al., 2010; Lundqvist et al., 2010; Løhaugen et al., 2010; Gibson et al., 2011; Chacko et al., 2013; Akerlund et al., 2013; Grunewald et al., 2013). Moreover, for the first time, there was a significant improvement in a more active working memory task (Following Instruction test), requiring to maintain and process information in memory during fine-motor control activities. Thus, PVL children increased both the span, that is the amount of information held in working memory, and the ability to control and process it. This result is in agreement with Diamond's recommendation that working memory must be continually challenged (Diamond et al., 2011), and suggests that an intensive and automatically adjusted training may be proposed to children with PVL in order to improve both storage and updating.

Several studies has documented CogMed generalization effects on non-trained tasks and everyday functioning (for a systematic review Melby-Lervag et al., 2013; Dunning et al., 2013; Spencer-Smith et al., 2015). The present study demonstrated the generalization of the training effects on the neuropsychological weaknesses that characterize PVL, in particular on visuo-spatial

processing and executive functions, as measured by the pre-post training tests. Significant generalization effects were found in tests of mental rotation, identification of spatial path inside a map, visual recognition of geometric forms, visual-spatial construction and phonological awareness. As these tasks require mental imagery, inhibition speed and information uploading, these findings suggest that the generalization of the training effects were specific to those visuo-spatial and language components requiring, more than others, executive functions such as cognitive control and flexibility.

This study thus provides new and relevant insights for implementing cognitive rehabilitation strategies in children with PVL. In fact, as working memory is a system necessary for holding and processing new and already stored information, it represents a transversal cognitive function, important for reasoning, comprehension and learning, which may influence cognition across-the-broad and induce cascade improvements on several neuropsychological processes. The finding of a near transfert effect to other impaired functions is particularly important in children with PVL where the neuropsychological impairment has a multilevel organization (Di Lieto et al., submitted). In fact one can speculate that, because of the empowerment of visuo-spatial and phonological processing abilities, the near transfer effect of working memory training may play a central role on mathematical and literacy achievements in PVL.

In order to further understand how working memory training affects performance in children with PVL, the study also analysed whether the training effects were influenced by the clinical characteristics of the sample, although this was beyond the scope of this study. No effects of chronological and gestational ages, intelligence level or gross motor functioning were found on the trained working memory outcomes (CogMed improvement index and Following the Instructions tests). These findings are in agreement with previous evidence describing gains in working memory capacity after CogMed training in different clinical populations, including preterm children (Grunewaldt et al., 2013) and across different ages (Klingberg et al., 2002; Thorell et al., 2009; Green et al., 2012; Løhaugen et al., 2012; Brehmer et al., 2012; Gropper et al., 2014). Moreover, the absence of correlations between the working memory improvement and gross motor impairments or intelligence suggests that all PVL children with an IQ from the borderline level and above (verbal IQ>80 inclusion criteria) may benefit from a working memory training. Conversely, the generalization effects on non-trained functions were found to be related to clinical characteristics. Gross-motor functions severity was related to the generalization effect in Imitation of hand position: children with severe gross motor impairment had greater gains with respect to those with mild motor impairment. Nevertheless, children with mild motor impairment took advantage from the training in visuo-construction tasks. Although preliminary, these results suggest

that by training transversal functions, such as working memory, children with motor disabilities tend to firstly ameliorate their most impaired function. A higher intelligence level, moreover, was related to a wider generalization effects on several non-trained functions with respect to lower intelligence level. Thus, the generalization effects of the working memory training may vary depending on the specific cognitive and clinical needs of PVL children.

In conclusion, this study suggests that a home-based working memory training in PVL children has a beneficial effect on trained working memory tasks as well as a generalization effects on visuo-spatial and language processes, especially for those subcomponents requiring cognitive control and flexibility. These seem to be an area of particular vulnerability in cerebral palsy due to PVL. Although larger studies and comparisons with other trainings are needed to confirm these findings, it may be speculated that working memory training is an effective intervention in school-aged children with bilateral cerebral palsy due to PVL in order to prevent or reduce cognitive problems that may negatively impact educational achievement and social functions.

Study 5

Effect of an adaptive working memory training on sleep slow waves activity in children with bilateral cerebral palsy and PVL: An high density EEG study

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Effect of an adaptive working memory training on sleep slow waves activity in children with bilateral cerebral palsy and PVL: An high density EEG study

Introduction

Periventricular Leukomalacia (PVL) is a white matter lesion surrounding the lateral ventricles of the brain occurring in the prenatal period, associated with a disorder of movement and posture, known as bilateral cerebral palsy. Children with PVL and bilateral cerebral palsy have generally spared verbal abilities, as measured by verbal intelligence quotient (verbal IQ) tests, while non-verbal intelligence and especially visuo-perceptual and visuo-spatial abilities are impaired (Fedrizzi et al., 1993; Ito et al., 1996; Yokochi et al., 2000; Sigurdardottir et al., 2008; Fazzi et al., 2009; Pavlova et al., 2009; Pavlova et al., 2013). In addition some studies have underlined the impact of PVL also on executive function, especially in terms of working memory and inhibition (Schatz et al., 2001; Pirila et al., 2004; Korkman et al., 2008; Jenks et al., 2009; Bottcher et al., 2009; Pirila et al.2011; Di Lieto et al., submitted).

Working memory is the ability to retain and manipulate information for brief periods of time. It is important in several complex cognitive functions, such as academic learning and in planning and organizing daily-life activities (Diamond et al., 2012; Wass et al., 2015). Recent behavioural and neurofunctional studies have described the effect of an evidence-based and computer-based training on working memory, the CogMed Working Memory Training. The behavioural findings have demonstrated the effect on working memory abilities and on cognitive functions not directly trained, as attention, inhibition, learning and non-verbal reasoning in several clinical conditions, such as ADHD (Klingberg et al., 2002; Beck et al., 2010; Gibson et al., 2011; Chacko et al., 2014), acquired brain injury (Lundqvist et al., 2010; Akerlund et al., 2013) and preterm birth (Løhaugen et al., 2010; Grunewaldt et al., 2013). Functional MRI studies on healthy adults have shown increase BOLD activities in parietal and prefrontal regions at the end of CogMed training (Olesen et al., 2004; McNab et al., 2009; Brehmer et al., 2011), indicating a training-induced neuroplasticity in the cortical systems underling working memory abilities. Neuroplasticity refers to the ability of the central nervous system to adapt to the changes external and internal environment (Huttenlocher, 2002) and is associated with structural and functional modifications in the brain which can be detected via neuroimaging and neurophysiological methods.

Investigating cerebral reorganization induced by working memory training is particularly important in children with congenital brain lesions, such as PVL, where cerebral plasticity is crucial as a compensative mechanism. Evidence is accumulating that sleep Slow Waves Activity (SWA,

electroencephalographic power between 0.5-4.5 Hz) is an efficient measure of cortical plasticity in humans because it reflects cortico-cortical connectivity (Huber et al., 2004; Hill et al., 2005) and it is regulated locally in a use- and experience- dependent manner (Kattler et al., 1994; Huber et al., 2000). Differences in topographical distribution of SWA have been reported during development. Slow Waves Activity, indeed, reflects plastic changes during brain maturation from early childhood through adolescence, showing a topographical shift of maximal SWA from more occipital (under 8 years) to frontal (from 11 years) areas along a developmental postero-anterior axis (Gogtay et al., 2004; Kurth et al., 2010). Moreover several studies have documented that the synaptic activity, induced in specific cortical region as consequence of daily-life stimulation, is reflected by SWA increase in the same brain area during sleep. The plastic changes in SWA in specific brain regions have been indeed found following learning processes both in adults and children (Huber et al., 2004; Landsness et al., 2009; Sarasso et al., 2014; Pugin et al., 2015). The local increase in SWA was found in right parietal cortex following a visuomotor adaptation training (Huber et la., 2004), in fronto-parietal networks following speech therapy in adults with left hemispheric stroke (Sarasso et al., 2014), and in left fronto-parietal networks following a visuo-spatial working memory training in healthy children (Landsness et al., 2009).

Investigating the plastic changes in SWA also in congenital neurological disorders, as PVL, may enhance knowledge on developmental and synaptic plasticity of a lesioned brain network. The aim of the study was thus to analyze the effect of the CogMed working memory program, an evidence-based training with documented effect on neural plasticity, on cognitive abilities and on changes in topographical distribution of SWA in a group of children with PVL. The second aim was to analyse the relationship between lesion characteristics, such as the lesion hemispheric asymmetry, and lateralization of the topographical distribution of SWA. The study intended to shed light on the mechanisms of neuroplasticity, by enhancing knowledge on the neuropsychological effects of a specific working memory training and on the neurophysiological underpinnings of these behavioural effects in a clinical population of children with congenital brain lesions. This study has been registered with ClinicalTrials.gov, numbers NCT02342990, in January 20, 2015.

Material and Methods

Participants

Thirteen children (7 females, 6 males) with bilateral cerebral palsy due to PVL (mean age 6.3 years, SD: 1.6 range: 4.1 – 9.0 years) and a mean gestational age at birth of 31 weeks (range: 28-37) were selected from a larger sample of children with cerebral palsy referred in the years 2014-2015 to the Department of Developmental Neuroscience of IRCCS Stella Maris Institute. Children were selected according to the following inclusion criteria: (a) neuroradiological diagnosis of PVL documented at brain MRI performed after age 2 years (by images or on neuroradiological reports), (b) level I to III at the Manual Ability Classification System (MACS- Eliasson et al., 2006), (c) absence of drug-resistant epilepsy (d) absence of a psychiatric disorder diagnosis or sensory deficits that preclude testing, (e) Verbal Intelligence Quotient above 80, as assessed by WPPSI-III (Wechsler, 2002), WISC-III (Wechsler, 1992) or WISC-IV (Wechsler, 2003) in the last year prior to recruitment. All children were native Italian speakers. The research project was approved by the Ethical Committee of IRCCS Stella Maris Institute (n° 13/2013). Written consent was obtained from all participants' parents who also gave informed consent to publication of results.

The Gross Motor Classification System (GMCS) (Palisano et al., 1997) was used to determine gross motor skills. Children were classified in five motor levels: walk without restriction (level I); walk without assistive devices but limitation in walking outdoors (level II); walk with assistive mobility devices (level III); self-mobility with limitations (level IV); self-mobility is severely limited even with use of assistive technology (level V).

The PVL lesion was classified according to hemispheric asymmetry of ventricular dilatation as documented by the neuroradiological report. The PVL lateralization was classified into three neuroanatomical conditions: R=L, when the involvement of right and left hemispheres were equivalent; R>L, when the right hemisphere was more damaged than the left; and L>R, when the left was more damaged than the right.

Intervention program

CogMed Working Memory Training (RoboMemo®, CogMed Cognitive Medical Systems AB, Stockholm, Sweden) is an home-based software to improve working memory deficits by computer games that progressively increase working memory demands. CogMed training contains a variety of computerized, game-format tasks that are adaptive, with level of task difficulty adjusted

automatically to match the working memory span of the child on each task. This training is available in three on-line versions based on the child's age. Almost all of children included in the study used CogMed RM version, for school-aged children, while three of them (S3, S7 and S11 in Table 1) used CogMed JM version, for pre-schoolers. The CogMed RM includes 12 visuo-spatial and verbal tasks, each session consists in eight tasks and lasts 45 minutes a day; the CogMed JM consists of 7 visuo-spatial and verbal tasks lasting 20 minutes a day. A training period of five weeks for a total of 25 sessions, was performed by each child at home. The same certified coach presented CogMed program to the child and his/her family, establishing with them a reward system, goals and treatment planning, followed the training progress and weekly called the families to give advice based on the uploaded results.

Study Design

As shown in Figure 1, a Stepped Wedge randomized trial design (Brown et al., 2006) was chosen to randomly split the children into two groups (Cluster A, n=8 and Cluster B, n=5), for sequential rollout of the training. There was no difference in chronological age and sex between the two Clusters.

At time point T0, neuropsychological tests and sleep hdEEG were performed for both Clusters. Children in Cluster B immediately started CogMed training, while those in Cluster A did not receive any training in the same period, continuing their daily life activities as usual. Six to seven weeks later, neuropsychological tests and hdEEG were again performed in both Clusters (time point T1). Then children in Cluster A started CogMed training and six to seven weeks later were retested with neuropsychological tests and examined with hdEEG (time point T2).

Figure 1

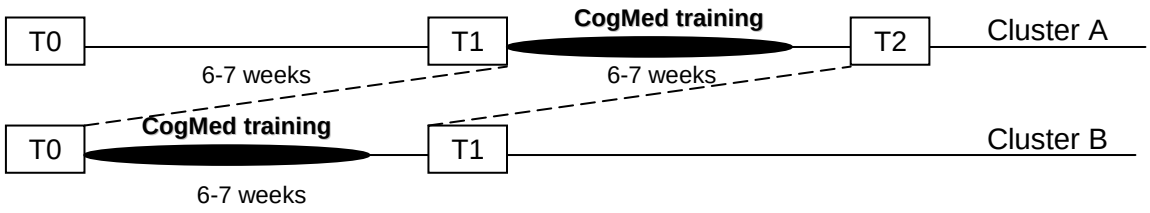

Figure 1: time points of the stepped wedge randomized trial design for the study of the patients divided in two groups, Cluster A and Cluster B.

CogMed indices and neuropsychological assessment

The CogMed Improvement index was provided by the program and calculated by subtracting the Start Index (the mean of the three best successful trials on days 2 and 3) from the Max Index (the mean of the three best successful trials on the two best training days). A CogMed Improvement Index greater than 14 (>1 SD) represented a significant improvement of WM abilities.

The following neuropsychological areas were assessed: Executive function/attention, Manual planning, Visuo-spatial memory and Visuo-spatial processing. For the mean area score only the subtests scores which improved significantly after the training were considered. All subtests were also expressed as raw scores for pre- and post- training comparisons.

The Executive functions/attention area was assessed by some subtests included in Executive Function/Attention and Language domains at the NEPSY-II (Korkman et al., 2007): Visual Attention, Auditory Attention and Response Set; Inhibition subtest and Phonological Processing.

The Manual planning area was tested by all the subtests included in the Sensorimotor skills domain at the NEPSY-II.

The Visuo-spatial memory area was measured by Memory for Design subtest included in the Memory and Learning domain at the NEPSY-II.

The Visuo-spatial processing area was evaluated by all the subtests of Visuo-spatial processing domain at the NEPSY-II.

The description of each subtest as it appears in the scoring form is reported in the “Structure and purpose of NEPSY-II” section included in the introduction of this Thesis.

Sleep hdEEG recording and analysis

High density EEG (hdEEG) sleep signals were recorded during a postprandial napping using a 128 channels system (Electrical Geodesics Sensor Net v1.0). Before each recording session, electrode impedances were measured to ensure that no sensor had impedance values higher than 50kΩ. The signal were sampled at 250 Hz and referenced to a vertex electrode for direct visualization, filtering and decomposition using independent component analysis (ICA). All analyses were computed using custom MATLAB (The Mathworks, Natwick Massachussetts) routines.

Signal was filtered using a first order highpass filter (0.01hz), a Butterworth bandpass filter (lowpass 30hz, highpass 0.5hz) and a second order infinite impulse response notch filter (50hz). Subsequently, EEG data were visually scored by an expert technician according to AASM (Manual for the Scoring of Sleep and Associated Events) standard criteria (Iber et al., 2007). All analysis refer to non-REM (NREM) N3 if not otherwise specified.

Bad channels were identified using a semi-automatic approach: all EEG data were visually inspected in order to identify channels affected by artifacts. After this visual rejection step, channels displaying spikes of amplitude greater than 10000uV were rejected, as well as the ones with a maximum amplitude < 0.1uV and/or with a distribution shift greater than 3.5 standard deviations compared to the mean distribution of the signal. Each automatically identified bad channel was visually inspected and reviewed. Rejected channels were interpolated using the spherical interpolation method.

Data from all electrodes were then decomposed using ICA. Extended-ICA algorithm (Lee et al., 1999) with optional PCA dimension reduction were used. ICA components were visually inspected in order to remove ocular, muscular and other artifacts from the EEG signal. ICA pruning outcome was compared to the source signal to ensure the least impact on non-artifact data. ICA pruned data were then re-referenced to the average of a subset of 109 electrodes: each sample was divided by the mean of all the electrodes, arranged in a radius <= 0.66 from the center of the reference.

Signal spectrum was calculated using the Welch method on 6 second epochs with a resolution of 0.17 Hz, using a Hamming window. Mean spectra of each 30 second epoch was calculated, and power of each epoch, for each channel, was divided by the mean power across all channels of that epoch. All 30 seconds epochs exceeding a power six fold greater than the average

power across channels of that epoch in the SWA band (1-4.5 Hz) or in the 20-40 Hz band were rejected.

All comparisons were matched to the shorter interval across recording sessions. As shown in Figure 1, nine arbitrary clusters of surface electrodes were identified. Cluster 1, 4 and 7 included electrodes localized on left frontal, parietal and occipital regions respectively; cluster 2, 5 and 8 included electrodes placed on frontal, parietal and occipital (median line); and finally cluster 3, 6 and 9 included electrodes placed on right frontal, parietal and occipital regions respectively; clusters were defined to include a similar number of electrodes.

Figure 2

	Left side	***Median line***	***Right side***
Frontal lobe	*1*	*2*	*3*
Parietal lobe	*4*	*5*	*6*
Occipital lobe	*7*	*8*	*9*

Figure 2: 9 arbitrary clusters used to represent SWA changes

Statistical analysis

Statistical Package for Social Sciences, version 13.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and MATLAB (The Mathworks, Natick, Massachussetts, USA) were used for the statistical analyses.

Mann-Whitney and t-test analysis were performed to verify differences between the two Clusters in intelligence levels, GMFCS, Start index and the pre-training neuropsychological areas and subtests. To verify test-retest effects in Cluster B (T0-T1, n=7) and the training effects in both Clusters (pre- post- training, n=13), the differences in the neuropsychological areas and subtests were analyzed by t-test analysis.

Paired t-tests comparing pre- and post-training were performed to detect the changes in SWA topography, that is where SWA had a higher spectral power with respect to the mean spectral power of all hdEEG channels. The extension of SWA changes was considered “widespread”, when

SWA changes were extended to frontal, occipital and parietal lobes, and was considered "localized", when SWA changes were restricted either to occipito-parietal or fronto-parietal lobes.

Bi-variate Pearson correlations were performed between each EEG cluster and the percentages of improvement for those neuropsychological areas showing significant training effects. The percentage of improvement was calculated dividing the difference between post- and pre-training performances by pre-training performance and multiplying it by 100. Chi square analysis was conducted to verify the association between the lateralization of SWA changes and the lateralization of the PVL lesion for each child. The lateralization of SWA changes was considered right or left for each lobe (frontal, occipital or parietal) in relation to the hemisphere where SWA power was higher than the mean SWA of all channels.

Results

Clinical characteristics of the sample are reported in Table 1.

Table 1

Clinical characteristics of PVL children

	Sex	**GA**	**Age** ***(y;m)***	**Lesion lateralization**	**Motor functions** ***GMFCS level***	**Intelligence Level** **Verbal***	**Non-Verbal***
S1	M	28	9;0	R>L	III	102	85
S2	M	28	6;0	R=L	II	88	93
S3	F	29	4;1	R>L	III	106	76
S4	M	31	5;1	L>R	III	108	82
S5	F	29	5;1	L>R	IV	114	104
S6	F	29	7;0	L>R	II	94	95
S7	F	30	5;1	R>L	II	100	82
S8	F	32	8;0	L>R	II	82	58
S9	M	31	8;1	L>R	II	104	87
S10	F	32	9;1	R=L	III	102	100
S11	F	32	6;1	R>L	IV	100	89
S12	M	37	6;0	L>R	I	124	111
S13	M	32	7;8	R>L	II	100	62
Mean (SD)	**-**	***31.0(2.4)***	***6;3(1;6)***	**-**	**-**	***102.6(11.0)***	***85.8(14.7)***

Note: GA, gestational age; R, right; B, bilateral; L left; GMFCS, Gross-Motor Function Classification System; verbal, Verbal IQ (WISC-III,WPPSI-III) or Verbal Comprehension Index (WISC-IV);non verbal*, Performance IQ(WPPSI-III) or Perceptual Organization Index (WISC-III) or Perceptual Reasoning Index (WISC-IV).*

At gross motor functioning assessment (GMFCS), 1 child was classified at Level I, 6 children at Level II, 4 at Level III and 2 at Level IV. As expected from the literature, almost all children (11 out of 13) had a verbal intelligence index greater the non-verbal. No significant differences between Cluster A and Cluster B were found in verbal and non-verbal indices ($t(11)=-1.21$, ns; $t(11)=-.23$, ns; respectively), in GMFCS ($Z=-1.04$, ns), in the Start CogMed index ($t(11)=-.24$; ns) and in any other neuropsychological area at pre-training assessment. Although all children had a bilateral congenital lesion, 11 children out of 13 showed a hemispheric asymmetry as one hemisphere was more affected than the other: the left hemisphere was more affected in 6 children and right in 5.

Training effects on neuropsychological processes after six/seven weeks of Working Memory training

The Max Index was significantly higher than the Start Index ($t(12)=-6.74$, $p<.001$) and a large effect size was found ($d=1.15$). The Improvement Index, indeed, was higher than the improvement cut-off value (mean 20.8; SD 11.5; range 8-52) and did not correlate with the Start max index ($r(13)=.37$, ns).

After the training, significant improvements were found in different neuropsychological subtests included in Executive function/attention, in the Visuo-spatial memory and in the Visuo-spatial processing areas. Significantly increments in performance were found with small effect size in speed (sec) in Inhibition subtests within the Executive function/attention area, with moderate effect size in Memory of Design subtest included in the Visuo-spatial Memory area, and with large effect size in Block Construction, Geometric Puzzle and Route Finding subtests within the Visuo-spatial processing area. No subtests included in the Manual planning area resulted significantly improved comparing pre- and post- training assessment (for details see Table 2). The following area scores for pre- and post- training assessment were calculated: Executive Function/attention area by the speed in Inhibition subtest; Visuo-spatial Memory area by the Memory for Design subtest; and Visuo-spatial elaboration area by Block Construction, Geometric Puzzle and Route Finding subtests.

Table 2

Neuropsychological subtests improving significantly after training

	Pre-training *Mean(SD) n=13*	***Post-training*** *Mean(SD) n=13*	***Within-subject significance of change*** ***t***	***df***	**p**	***Cohen's d***
Executive Function/attention area						
speed (sec) in Inhibition	*169.9(70.6)*	*151.4(58.5)*	*2.25*	*10*	*.049**	***.3***
Visuo-spatial Memory area						
Memory for Design	*59.9(27.8)*	*72.5(32.1)*	*2.17*	*12*	*.050**	***.5***
Visuo-spatial processing area						
Block Construction	*7.9(2.3)*	*9.5(2.2)*	*3.64*	*11*	*.004**	***.7***
Geometric Puzzle	*15.4(5.8)*	*18.5(6.2)*	*3.39*	*11*	*.006**	***.5***
Route Finding	*1.7(1.5)*	*3.9(2.7)*	*3.09*	*9*	*.013**	***.9^***

Note: *Significance after Bonferroni's Correction ($p < .05$); ^large effect size (Cohen's d > |.8|)

Changes in sleep SWA topography and neuropsychological correlations

The changes in SWA topography, comparing SWA pre- and post- training, and the 9 arbitrary clusters of surface electrodes for each child are shown in Figure 3. Visual inspection of the figure reveals different changes in SWA topography at the end of the training in frontal, parietal and occipital regions in 9 out of 13 children (S1, S2, S4, S5, S8, S9, S11, S12, S13), in parieto-occipital regions in 2 children (S3, S10) and in fronto-parietal regions in 2 (S6, S7).

Figure 3

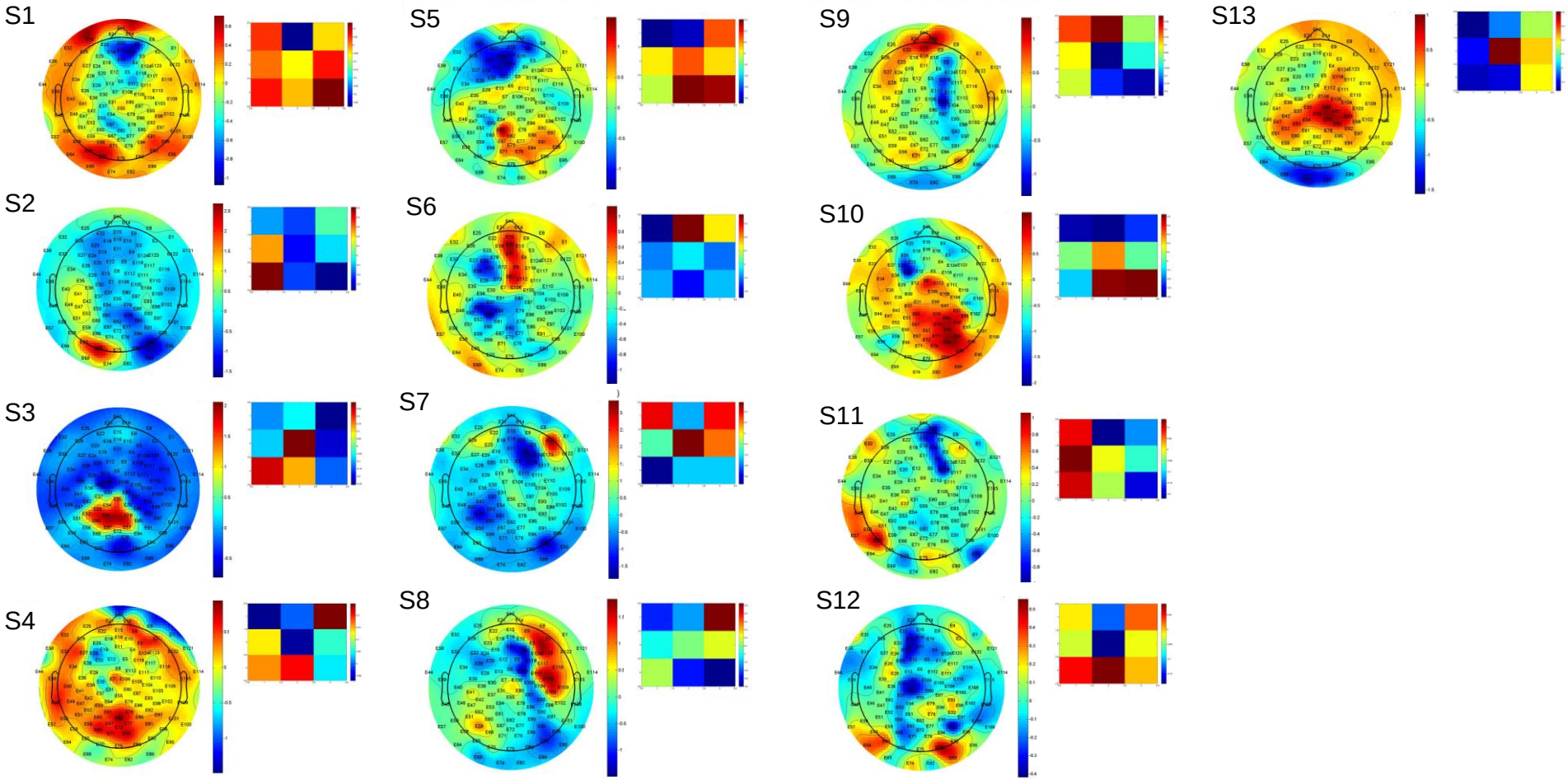

Figure 3: The changes in SWA topography and in arbitrary clusters (3X3) for each child compared pre- and post-training hdEEG session. The changes in SWA is color coded: maxima in red, minima in blue.

The percentage of improvement in Executive Function/attention, Visuo-spatial Memory and Visuo-spatial processing areas were correlated to the SWA changes in each cluster. Significant positive correlations were found between the percentage of improvement in Executive Function/attention area and the SWA changes in cluster 2 (frontal medial line region) ($r(11)=.59$, $p<.05$) and the percentage of improvement in Visuo-spatial processing and the SWA changes both in cluster 3 (right frontal region) and 6 (right parietal region) ($r(10)=.75$, $p<.01$ and $r(10)=.63$, $p<05$ respectively) (Figure 4).

Figure 4

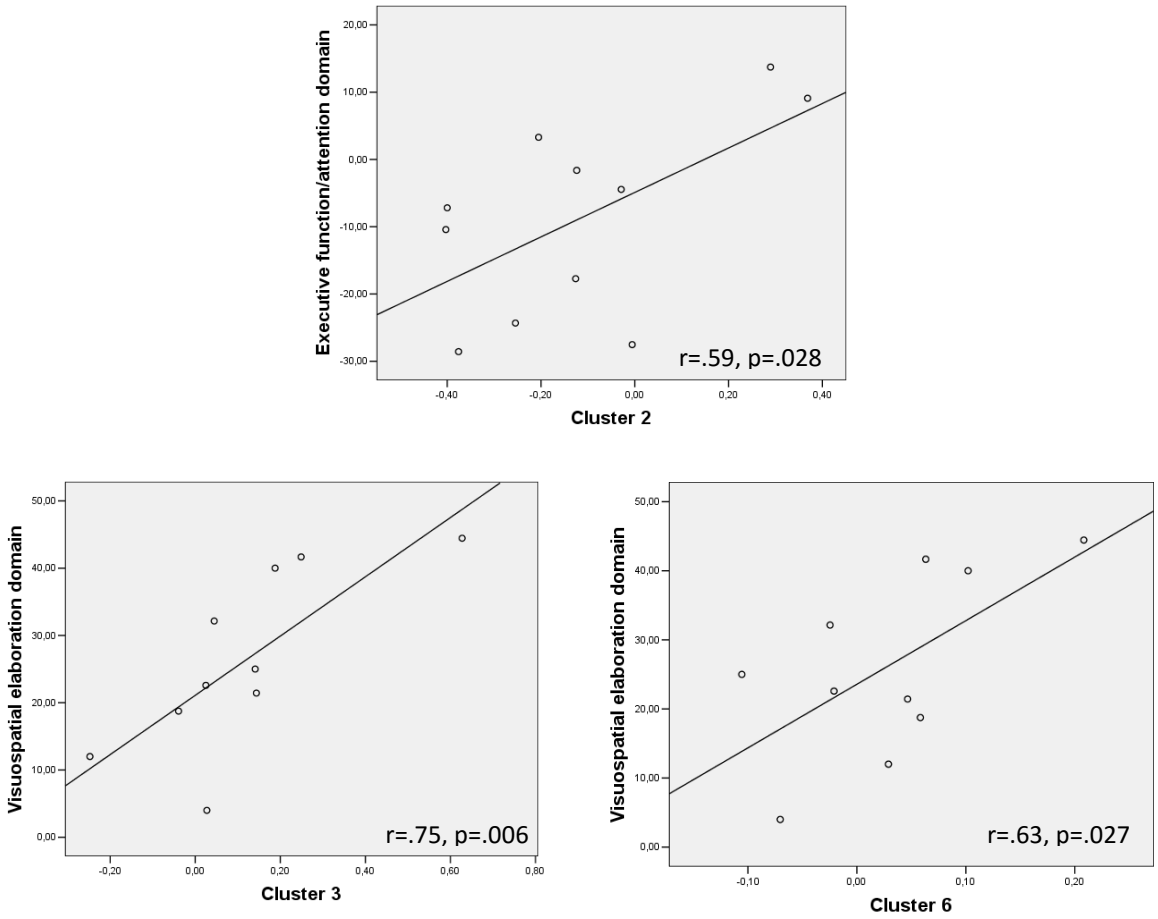

Figure 4: SWA changes in hdEEG clusters significantly correlated with neuropsychological areas

Chi-square analysis revealed a significant association between the lateralization of PVL lesion (extension more lateralized in left or right hemisphere) and the lateralization of SWA changes in right or left frontal clusters (cluster 1 or 3) ($\chi^2(1)=4.4$, $p<.05$), as more extended PVL lesions in left regions showed an higher SWA in right frontal cluster at the end of the training.

Discussion

The present study is the first to describe the neurophysiological correlates of an intensive working memory training in children with congenital brain lesions. The challenge faced by clinicians and rehabilitators in the face of early brain injury is to understand how to optimally engage and modify surviving neuronal networks, that is, neuroplasticity, to provide new response strategies that can compensate for tissue lost to injury (Murohy et al., 2009). Although several recent studies had documented the effect of motor rehabilitation trainings on central nervous system modifications in children with stroke or brain lesion (for review Novak et al., 2013), less is known on the effect of cognitive training on the mechanisms underlying neuroplasticity a knowledge crucial for targeted interventions for children with brain injury (Johnston, 2009).

Given the crucial role of Slow Waves Activity in cortical plasticity, this neurophysiological measure was considered a direct indication of potential training-induces changes of the central nervous system after congenital brain lesion. The novel contribution of this study was thus to describe the changes in SWA topography and neuropsychological correlates after a working memory training in a group of children with PVL.

The main finding of the study was that after a working memory training, SWA topography changes shifted to the parietal lobe in all children and to fronto-parietal-occipital network in almost all children. This general result supports other evidence that sleep SWA, reflecting the depth of sleep, is regulated in a use- and experience dependent manner and thus reflects cortical plasticity (Kattler et al., 1994; Huber et al., 2004; Sarasso et al., 2014; Pugin et al., 2015). Moreover the localization of SWA changes is in agreement with the studies documenting neurofunctional changes after working memory training in terms of a significant increase of the BOLD activity in fronto-parietal networks (Olesen et al., 2004). These studies, however, were conducted on healthy adults rather than on children with congenital lesions and, by using BOLD activity measures, they could not pinpoint which processes drive the neuroplastic changes observed after training. By analyzing SWA, it can be hypothesized that working memory training induces synaptic consolidation by increasing synaptic strength and density (Tononi et al., 2006), thus synchronizing the activity of the fronto-parietal-occipital network (Kurth et al., 2010).

The correlations between the changes in SWA topography and the neuropsychological improvements after the training is another important finding of the present study. In fact, significant associations were found between the improvement in the areas of executive functions and attention and SWA changes in both right-frontal and parietal regions. These data suggest a cortical reorganization mainly found in the right fronto-parietal network and are particularly

important given the neuropsychological profile and neuroanatomical correlates which characterize children with PVL. It is in fact known that in this clinical population visuo-spatial and executive function weaknesses may characterized the neuropsychological profile and are associated to PVL lesions more extended both to frontal and occipital lobes (Di Lieto et al., submitted). For the first time it has been postulated that beside a cortical reorganization resulting from sensory and motor interventions (Novak et al., 2013), cortical plasticity may also be induced in PVL children by reinforcing the fronto-parietal regions spared by the lesion.

As expected, cortical plasticity followed an inter-hemispheric reorganization because it was lateralized in the less lesioned hemisphere. Indeed, all children with the left hemisphere more damaged than the right, showed SWA changes in the right frontal lobe, suggesting the engagement of non lesioned neuronal networks to provide new response strategies that compensate the cortical tissue lost to injury. Several studies on other congenital brain lesioned populations, such as left perinatal stroke, documented the neuroplastic reorganization of language functions in homologous areas in the right hemisphere during development (Carlsson et al., 1992; Isaacs et al., 1996; Brizzolara et al., 2002; Chilosi et al., 2005; Guzzetta et al., 2008), confirming the role of inter-hemispheric reorganization in functional recovery

Whereas SWA changes may be influenced also by other lesion characteristics, such as the extension, larger groups of children and further analysis are needed to verify other potential associations between cortical reorganization after working memory training and neuroanatomical characteristics.

CONCLUSIONS AND FUTURE PERSPECTIVES

CONCLUSIONS AND PROSPECTIVES

In order to further the understanding of the neuropsychological profile of a complex neurodevelopmental disability, such as bilateral cerebral palsy due to PVL, this PhD thesis is based on a multifaceted approach that integrates different levels of description which often are separately investigated. The findings of the five studies presented in the thesis tightly interconnected confirm the importance of using such an investigative approach for improving clinical care and treatment.

The neuropsychological findings described in Study 1, suggesting the presence of specific deficits in executive functions in a subgroup of children with PVL, deserve to be followed by future longitudinal studies. Follow-up measures may, indeed, investigate whether such neuropsychological profile follows a developmental trend according to which weaknesses or strengths emerge across ages. Moreover further research aimed at describing executive function deficits in children with PVL, may take into account the evidence that some sub-component of executive functions are spared. The results of Study 1, moreover, may provide important insights for defining a novel clinical assessment protocol for children with PVL, integrating scientific research data with clinical needs. It clearly emerges, indeed, that beyond the assessment of visuo-spatial and motor abilities, a clinical protocol requires evaluating also specific components of executive functioning, such as inhibition, speed of processing and updating.

The findings of Study 2 and 3, underline the importance of also assessing behavioural and emotional profiles in children with PVL, by parent report measures (CBCL checklist), as well as academic achievement. Thus, an exhaustive clinical protocol should also focus social withdrawal and somatic problems and to reading text comprehension and maths and that can influence future social, adaptive and vocational functioning in this clinical condition.

A comprehensive clinical protocol, addressing all weaknesses found on account of the integration of several levels of description (e.g. neuropsychological, psychopathological and academics) may represent a good evidence-based clinical practice oriented to the needs of children with PVL.

The possibility to combine neuroanatomical/neurophysiological and neuropsychological data, on one side, and behavioural and cognitive outcome after a training, on the other, has been crucial, during the PhD period. It has provided evidence on the neurofunctional correlations of neuropsychological and emotional/behavioural profiles as well as indicated that neuropsychological rehabilitations in children with PVL. The findings of Study 4 and 5 reveal the benefits of an intensive cognitive training on working memory and executive functions and its association to the cortical reorganization of a spared fronto-parieto-occipital network in children

with PVL. The expected improvement may be, nevertheless, considered as a general short-term cognitive empowerment, requiring long-term consolidation and generalization to academic achievement. The implementation of follow-up assessments and other psychological therapies or cognitive rehabilitations specifically oriented to the single patient's needs, are particularly important in this complex disorder. From the findings, future research may integrate sleep hdEEG and fMRI data in order to clarify the relationship between the cerebral reorganization during sleep in the occipito-parieto-frontal network, and the neurofunctional activation in fMRI, after working memory training in PVL.

The multi-faceted approach used in this PhD thesis may also be extended to other complex disorders to further our understand the neurofunctional profile to favoured by the current expansion in information technology, such as the adaptation of compensatory devices and the virtual reality, also applied to school education. Neuroscience challenges the discipline of education to employ research on the neural factors which influence learning efficiency. Until recently these two disciplines, education and neuroscience, have proceeded in parallel with little or no collaboration. However, advances in both disciplines are leading to greater convergence of scopes making the emerging field of "Educational Neuroscience" a necessary area of study for the comprehensive care of children with complex neurodevelopmental disabilities addressing both rehabilitation and educational needs.

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