Visuospatial attention deficits in children with unilateral cerebral palsy

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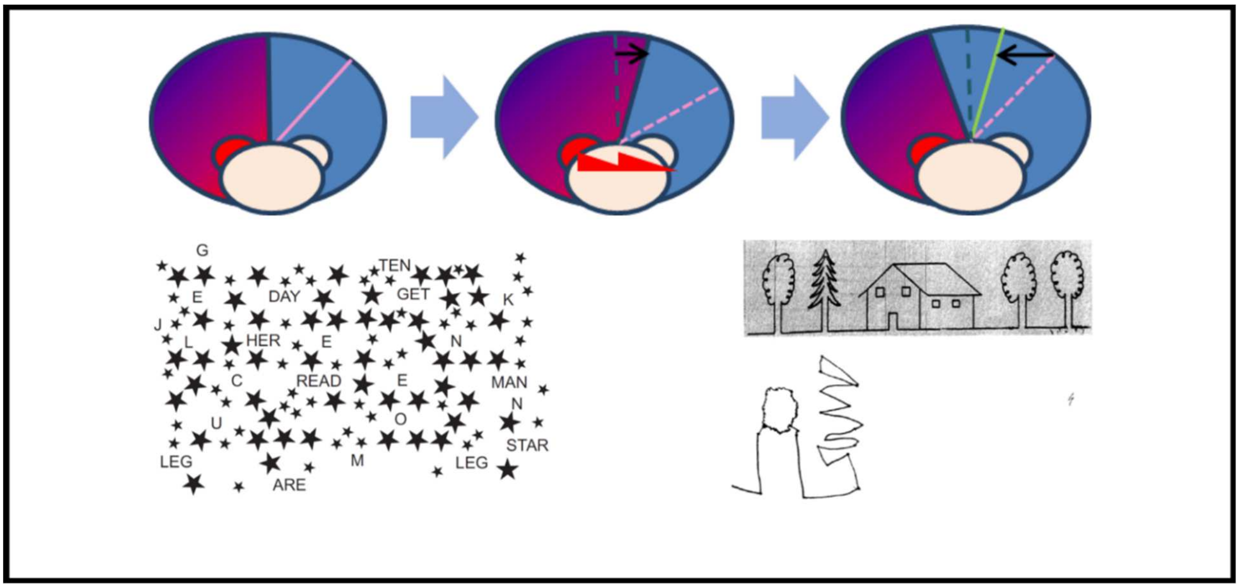

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Chapter I: General introduction

Attention refers to the collection of mechanisms that selects which of many possible stimuli to process and to act on (Smith and Chatterjee, 2008). Classically, three different conceptual systems, the alerting, orienting and executive systems (Petersen and Posner, 2012; Posner and Petersen, 1990), are involved in attentional processing, each including a different set of attentional processes. Visuospatial attention, defined as the ability to orient to salient visual stimuli and to parse the visual world, is part of the orienting network (Petersen and Posner, 2012).

The orientation towards stimuli – processed by the orienting network – can be endogenous or exogenous. In endogenous orientation, or task driven orientation, the orientation towards a stimulus is based on the task carried out by the subjects. Someone looking in a crowd for a friend wearing a red hat (or for Waldo) will orient his or her attention endogenously (Corbetta and Shulman, 2002). However, if a police light starts to flash, the attention of the person will orient itself towards the source of the light, which is an exogenous orientation of attention. Indeed, in this case, orientation of attention is driven by the salience of the stimuli or stimuli driven (Corbetta and Shulman, 2002; Hayward and Ristic, 2013). Some studies highlighted the possibility to elicit separately endogenous and exogenous stimuli showing that the orienting conceptual network referred to two cortical networks: 1) a dorsal frontoparietal network involved in endogenous orienting of attention 2) a ventral frontoparietal network involved in exogenous orienting of attention, the ventral network being more right lateralized than the dorsal network (Corbetta and Shulman, 2002). This early model of visuospatial orientation has shown little evolution since its proposition in 2002. Most of its evolution is related to a better understanding of the ventral network of attention orientation which seems less related to exogeneous orientation of attention than to a reorienting of attention towards new significant stimuli. According to these new findings, the authors proposed a revisited model of attention orientation which underlined the importance of the middle frontal gyrus during attention reorientation (Corbetta et al., 2008) (Figure 1A).Brain areas more related to the dorsal network are the intraparietal sulcus (IPs), the frontal eyes fields (FEF) while the temporoparietal junction (TPJ), the ventral frontal cortex (VFC) and the middle frontal gyrus (MFG) are more related to the ventral network (Figure 1B). Both networks present a rightward lateralization.

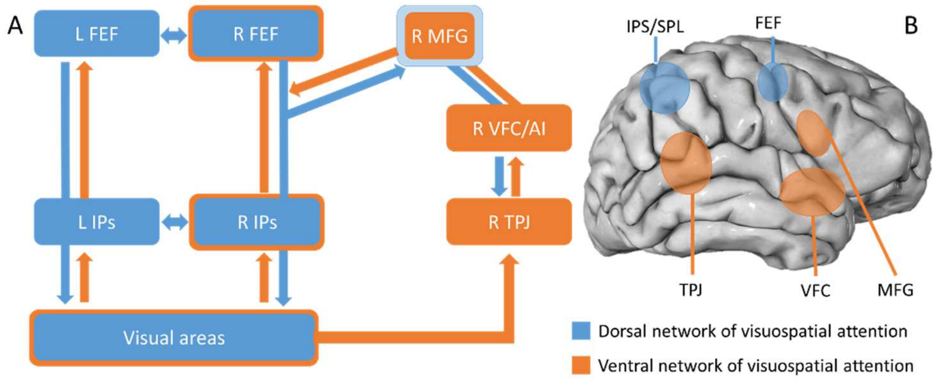

Figure 1: A) Model of attentional control adapted from Corbetta et al. (2008): Blue squares and arrows represent cortical areas and their connections involved in the dorsal network of attention control while orange squares and arrows represent cortical areas and their connections involved the ventral network of attention control.
B) Localization of the different areas linked to: the ventral network of attention in orange; the dorsal network of attention in blue.
FEF: frontal eye field; Ips: intraparietal sulcus; MFG: middle frontal gyrus; SPL: superior parietal lobule; TPJ: temporoparietal junction; VFC: ventral frontal cortex.

In this thesis, we focus on deficits of visuospatial attention relying on the orienting network, and more specifically visuospatial neglect. Visuospatial neglect can be related to impairments in both endogenous and exogenous components of visuospatial attention (Corbetta and Shulman, 2011). The cortical areas specifically associated with neglect are the ventral areas and the temporo-parietal junction.

Spatial neglect is an umbrella term characterizing a lateralized deficit of interaction between body and space with regards to different sensory modalities (tactile, proprioceptive, and visual). Visuospatial neglect describes the lateralized deficit of attention towards visual stimuli. This neglect can occur in different spaces/distances and can be directed towards different frames of references. Existence of different spaces and frames of references has been highlighted by dissociation of neglect

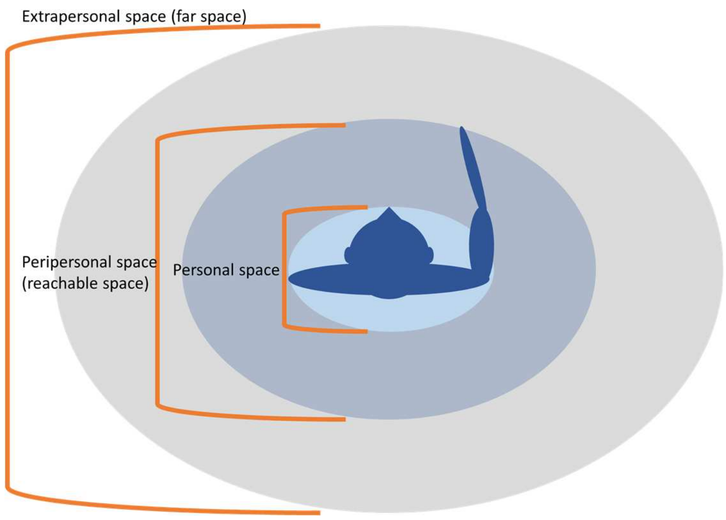

Figure 2: representation and extend of the different space in visuospatial attention.

symptoms in patients with brain lesions as well as by dissociation in response patterns in healthy subjects (Halligan and Marshall, 1991; Keller et al., 2005).

Space of representation

Three different spaces are considered when studying neglect: personal, peripersonal and extrapersonal (Berti et al., 2001; Beschin and Robertson, 1997; Halligan et al., 2003). These three spaces and their boundaries are illustrated in Figure 2. The personal space is defined as the human body including the surface of the person’s skin, the person’s face, his/her clothes. The peripersonal space refers to the space located within the arm’s reach of someone. It matches the space in which people interact directly with objects. The extrapersonal space, also called far space, is located outside the limits of the peripersonal space.

The peripersonal space may present with some specific properties according to the context in which it is studied. Brozzoli et al. (al., 2012) reported that the peripersonal space could be a body and limbs centered representation of the space or a multisensory interface for interactions with objects. These authors also reported that the representation of the peripersonal space might be important during avoidance reaction (fight or flight) and that the representation of the peripersonal space could be remapped specifically during actions execution. More recent studies make a distinction between the peripersonal space for goal directed actions and the peripersonal space for protection (de Vignemont and Iannetti 2015). In this thesis, when referring to the peripersonal space we refer to the space surrounding the person in which goal oriented actions, similar to actions needed during activities of daily living, are performed.

The limits of peripersonal and extrapersonal spaces are not fixed and can vary from one person to another depending on the arm length or limitations due to movement restriction. Several previous studies also highlighted that the use of tools can extend the limits of peripersonal space as the tool can increase the length of the arm and thus the reachable space (Gamberini et al., 2008; Longo and Lourenco, 2006). This phenomenon was illustrated by Gamberini et al. (2008) in real and virtual space using a line bisection task in healthy subjects. This task consists in line bisections with either a laser pointer or a wooden stick. The authors showed that when using a laser pointer to bisect lines, the response pattern changed between near (until 60 cm away from the subject) and far space (distance of 90 and 120 cm away from the subject). However, when using a wooden stick to bisect the lines, the response pattern remained the same in near and far space underlying the extension of peripersonal space by the use of a wooden tool.

Several studies have shown a possible dissociation in the impairments observed depending on the space in which stimuli are presented. Vuilleumier et al. (Vuilleumier et al., 1998) reported the case of a patient with a right temporal hematoma, presenting deficits in a cancellation task (crossing target stimuli among distractors) as well as in a line bisection task (cutting a line in two equal parts) in the extrapersonal space but not in near space (personal and peripersonal space). In the near space condition, tests were presented on a sheet of paper in front of the patients who responded using a pencil, while in the far space condition, tests were presented on a white screen (stimuli had the same visual angle size in both conditions) and patients responded using a laser pointer. In a study evaluating a functional scale for neglect, Zoccolotti et al. (1991) reported the case of a patient showing more severe impairments in the personal space than in the peripersonal space. Another study by Keller et al. (2005) reported a change in tests results depending on their presentation in the near or far space. They reported that patients with neglect increased their error in the line bisection test in the far space compared to near space, while their number of omissions in the cancellation task remained identical. In addition, the visuospatial attention in these different spaces have a significant impact on the sensorimotor function (Balslev et al., 2013; Chatterjee, 2003).

As most manual abilities are performed in the peripersonal space, an impairment such as visuospatial neglect may play an important role in neurological motor disorders (e.g. stroke, cerebral palsy) and their rehabilitation process. This thesis focusses on the study of visuospatial attention in the peripersonal space defined as the space where goal oriented actions occur.

Frame of reference

Neglect can be present in two different frames of reference, the ego- and allocentric frames (Halligan et al., 2003; Walker, 1995). In egocentric neglect, patients will neglect stimuli presented on one side of their body midline, while in allocentric neglect, patients will neglect stimuli presented on one side of an object midline (Figure 3). The egocentric representation is important for movement planning and motor control during interaction between body and objects, while the allocentric representation is important for determining spatial reference in the environment (Burgess, 2006; Colby, 1998). Several previous studies and case reports highlighted the dissociation between ego- and allocentric neglect (Halligan et al., 2003; Ota et al., 2001; Walker, 1995). Walker et al. (1995) in their review reported the case of patients presenting either egocentric neglect, allocentric neglect or a combination of both. They reported the results of studies in which patients asked to copy a drawing were omitting objects located on the left side of the drawing. On the other hand, Walker et al. (1995) also reported the case of a patient who, in the same task, only copied the right part of each object of the drawing independently of its position, neglecting the left part of each objects (allocentric neglect). In another study, Ota et al. (2001) reported a dissociation between ego- and allocentric neglect using a cancellation task. In their task, stroke patients were asked to circle complete circles or triangles and to cross incomplete circles or cropped triangles. They showed that some patients were neglecting the target stimuli presented on one side of the sheet of paper (demonstrating the presence of egocentric neglect) while others were circling incomplete circles (or cropped triangles) in addition of full target stimuli independently of their localization on the sheet of paper (demonstrating the presence of allocentric neglect).

Both ego and allocentric neglect in the peripersonal space are likely to interfere significantly with the manipulation and thus the everyday life activities of individuals with brain damage.

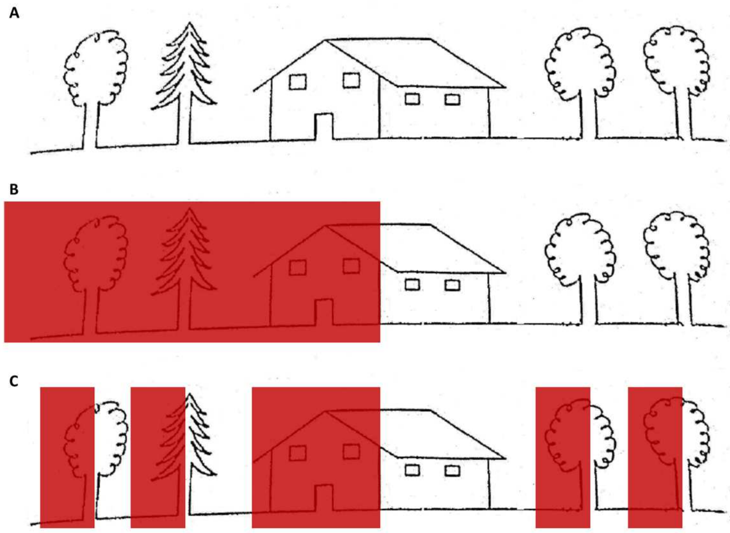

Figure 3: Illustration of ego- and allocentric error in the Ogden figure copy, red areas represent areas of the figure omitted by the patients. (A) The figure to be copied by the patient. (B) Copy with egocentric errors of copy, (C) Copy with allocentric errors of copy.

Several studies investigated the anatomical substrate related to the presence of neglect in adult stroke patients (Figure 4). Visuospatial neglect results from brain lesions, most of the time right brain lesions, localized in the parietal and temporal cortex. In a recent review, Chechlacz et al. (Chechlacz et al., 2012a) reported that neglect is associated with lesions of the inferior parietal cortex, the pre- and postcentral gyrus, the supramarginal gyrus as well as lesions of the superior temporal gyrus, the angular and middle temporal gyri, the middle occipital gyri, subcortical areas as the thalamus, and the basal ganglia (Figure 4). Lesions of the superior and inferior longitudinal fasciculus as well as of the inferior fronto-occipital fasciculus have also been associated to visuospatial neglect. As neglect can present as different subtypes, as illustrated above, the distinction between the brain substrates related to ego and allocentric neglect has been investigated. In an adult stroke sample, Chechlacz et al. (2010)

highlighted a difference between the neural structures underlying ego- and allocentric neglect: egocentric neglect was related to the fronto-parieto-temporal network and allocentric neglect to the parieto-temporal-occipital network. Other studies showed that egocentric neglect appears to be linked predominantly to the dorsal visual pathways while the allocentric neglect may be related to the ventral visual stream (Corbetta and Shulman, 2011; Medina et al., 2009).

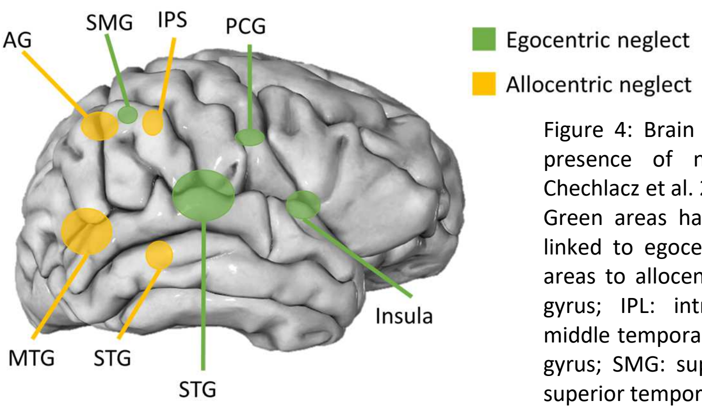

Figure 4: Brain substrates linked to the presence of neglect as reported in Chechlacz et al. 2012.
Green areas have been reported to be linked to egocentric neglect and yellow areas to allocentric neglect. AG: angular gyrus; IPL: intraparietal sulcus; MTG: middle temporal gyrus; PCG: post central gyrus; SMG: supra marginal gyrus; STG: superior temporal gyrus

Several reviews report a percentage of around half of patients with brain lesion experiencing neglect after a stroke (Bowen et al., 1999; Buxbaum et al., 2004; Nijboer et al., 2013a). However, the initial number of patients presenting neglect decreases during the months following stroke. Nijboer et al. (2013a) showed that after 12 weeks, 54% of the stroke patients with neglect showed sign of recovery while they were 60% after 26 to 52 weeks. Another study by Karnath et al. (2011) showed that after more than 1 years, 76% of the patients recovered from neglect. Thus of the around 50% of stroke patient showing symptoms of neglect around the stroke onset, more than half recover spontaneously in the year following stroke. A higher percentage of patients with a right brain lesion present neglect compared to patients with a left brain lesion (Bowen et al., 1999). Therefore, most studies investigating neglect in stroke patients have done this in right-lesioned patients with few including left-lesioned patients or with only a small percentage of left lesioned patients in the total sample. Nevertheless, recent studies highlight the presence of minimal neglect in left-lesioned patients by using dual tasks assessments, even though less detectable than in right-brain damage. Indeed, Blini et al. (2015) reported the presence of right neglect in patients with left hemisphere lesions using a computerized task. The patients from their study did not show neglect when tested with widely used cancellation tasks but did so in the dual tasks condition.

Historically, two hypotheses have been proposed to explain the lateralized deficit of neglect and the higher occurrence of neglect in patients with right brain lesions. According to the first hypothesis, both brain hemispheres control the attentional shift towards the contralateral hemispace, but the right hemisphere is additionally involved in the control of attention towards both hemispaces. Thus, in case of a right brain lesion, a shift of attention toward the right hemispace will occurred while in case of a left brain lesion, the right hemisphere can compensate for the damaged left hemisphere.

A second hypothesis, the inter-hemispheric competition hypothesis, proposes that the left and right hemispheres orient attention towards the contralateral hemispace but that the left hemisphere exerts a stronger bias. In this case, there is a reciprocal inhibition balance between both hemispheres. A right brain lesion would lead to the attentional imbalance observed in neglect. In the case of a left brain lesion a smaller attentional imbalance would be present and may be less detectable.

Previous anatomical studies reported that the brain lesions inducing neglect are mainly located in the ventral networks. Corbetta et al. (2005, 2008) hypothesized that a lesioned ventral network could send an altered “circuit breaking” signal to the dorsal network during target detection and attention re-orientation as well as reduce activity in the right dorsal network. This could cause a hemispheric imbalance in attention, leading to impaired attention shifting and thus neglect. More recently, Zuanazzi et al. (2017) studied the question of the influence between brain hemispheres in neglect by investigating the effects of TMS on the right parietal lobe following (test group) or not (control group) modulation of the excitability of the left parietal lobe using tDCS in a line bisection test. The authors found that TMS applied on the right hemisphere produced neglect like deficits in healthy subjects. They also reported that no effect of tDCS was observed in the condition associating TMS and tDCS. tDCS alone on the left hemisphere produced a deficit of spatial attention towards the left hemispace. Their results can be explained by the hypothesis advanced by Corbetta et al. (2005; 2011) of a bilateral representation of the dorsal network and a right lateralized ventral network inhibiting the dorsal network.

Based on these experimental data, the hypothesis of an interhemispheric imbalance phenomenon appears as most plausible to explain neglect in patients.

The high prevalence of neglect among stroke survivors is problematic. Indeed, presence of neglect may lead to a decrease in Activities of Daily Living (ADL) performance in patients. These patients will neglect most of the stimuli presented on their contralesional side leading to difficulties in different usual tasks, easily carried out by participants without neglect. These deficits often are strengthened by anosognosia (Buxbaum et al., 2004). Inside their houses, some patients collide with walls/obstacles which they do not “see”. It has been reported that patients suffering from serious neglect may only eat half their plates or shave only half their faces. To increase the functional independence of patients with neglect in everyday life activities, several rehabilitation strategies of visuospatial neglect have been developed and some of them have demonstrated their efficiency. Three systematic reviews investigating rehabilitation strategies for visuospatial neglect used in adult stroke patients reported the efficacy of 3 specific interventions: visual scanning training, limb activation and prismatic adaptation.

These interventions have shown the best efficiency to decrease neglect symptoms and increase independence in daily life activities (Kerkhoff and Schenk, 2012; Luauté et al., 2006a; Priftis et al., 2013; Yang et al., 2013). The latter two reviews suggest more evidence for prismatic adaptation (Kerkhoff &Schenk, 2012; Yang et al. 2013). Visual scanning training is a top-down intervention, which has been developed since 1970. In visual scanning training, patients are trained to orient their attention and to explore the neglected side of space using visual cues and feedbacks during different tasks as picture scanning, or copying. Limb activation is a bottom-up intervention using behavioral compensation. In limb activation therapy, patients are asked to initiate movement and carry on action with their contralesional limb in their neglected hemispace. In the last technique, prismatic adaptation, patients wear prismatic glasses inducing a visual field lateral shift towards the non-neglected side. While wearing the prismatic glasses, patients are asked to point to targets presented in their environment and compensate for the error induced by the prisms leading to a recalibration of sensory-motor coordinates. When they remove the glasses, this recalibration induces an after effect towards the neglected side. These three different therapies are currently used in the treatment of neglect in adult patients (Luauté et al., 2006b; Priftis et al., 2013; Rossetti et al., 1998).

Though both clinical observation and neurophysiological substrate of neglect in stroke patients are now largely documented, visuospatial attention deficits in congenital brain lesions are less documented.

<u>Visuospatial attention in children with cerebral palsy</u>

Cerebral palsy, due to brain damage occurring during the prenatal, perinatal or early postnatal life (up to 2 years old), is the most frequent pediatric motor disability affecting 2 to 3.6 per thousand live births (Pakula et al., 2009; Yeargin-Allsopp et al., 2008). Besides the motor deficit characterizing cerebral palsy, children with CP can present associated sensory or cognitive impairments (Pakula et al., 2009; Shevell et al., 2009; Wichers et al., 2005; Yeargin-Allsopp et al., 2008). Among those, visuospatial attention deficits have been described in children presenting with Unilateral Spastic Cerebral Palsy (USCP).

USCP is one of the most common forms of cerebral palsy, representing up to 34% of all cases. In 2003, Trauner et al. (2003) reported the presence of neglect in children with USCP. This study used a task in which toddlers/children were shown a board on which toys were positioned. The localization of the toys touched by the children was recorded. The authors found that children with USCP were omitting toys presented on their contralesional side, highlighting the presence of neglect in 66% of their sample. Another study by Laurent-Vannier et al. highlighted the presence of neglect in 17% of children with a brain lesion they tested using a childfriendly cancellation task (Laurent-Vannier et al., 2006). In comparison to adult stroke patients which present acquired brain lesions, children with USCP suffered from perinatal brain lesions classified by their timing of occurrence. Cortical malformation occurred during the first and second trimester, periventricular white matter lesions occurred from the late second trimester to the beginning of the third semester while cortico-subcortical lesion occurred around the end of the pregnancy (Krägeloh-Mann and Horber, 2007). The mechanisms underlying recovery are different in children than in adult patients notable because of the larger reorganization possibilities, including the potential reorganization of different tracts in children with CP. This may lead to differentiated impairments between children with CP and adult stroke patients. About neglect, in contrast to studies in adult stroke patients, where a right brain lesion is mostly responsible for neglect emergence, these studies in children with USCP reported the presence of neglect in children with a left or a right lesion (Trauner, 2003). This finding could be explained by the “crowding hypothesis”: a shift of the language function, normally left lateralized, to the right hemisphere following a left hemispheric lesion, leading to less brain substrate available for the development of visuospatial attention and therefore inducing visuospatial deficits (Guzzetta et al., 2008; Lidzba et al., 2006). This hypothesis is sustained by a study of Lidzba et al. (2006) highlighting a correlation between the presence of neglect and the reorganization of language areas in the right hemisphere in children presenting a pre- or perinatally acquired left brain lesion. This hypothesis is illustrated in Figure 5.

Few studies investigated visuospatial neglect in children with congenital brain lesions and the tests and tasks used, up to now were dedicated to the measure of egocentric neglect solely (cancellation tasks) and did not assess allocentric neglect. It is thus still unknown whether children with USCP present deficits in measures of allocentric abilities too and whether this deficit is related to egocentric observations. This is especially important since both ego and allocentric neglect in the peripersonal space may interfere with manipulation abilities and functional abilities of children in everyday life. Furthermore, the heterogeneity of brain lesions in children with USCP and the following brain reorganization could lead to dissociations between ego- and

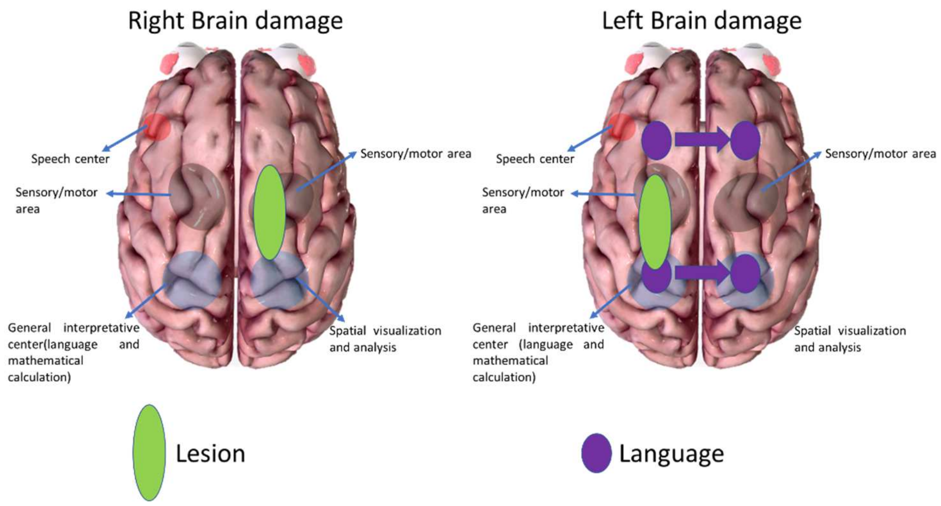

Figure 5: Illustration of brain (re)organization occurring after a right and left brain damage concerning the visuospatial and language areas.

allocentric neglect in children with USCP. In this context, testing only the egocentric aspect of neglect could thus lead to underestimate the prevalence of visuospatial deficits in these children.

As explained above, visuospatial neglect exists in children with unilateral cerebral palsy. The presence of visuospatial neglect in children with USCP may impair their ADL. Indeed, as most children with CP (up to 90%,) present with sensory and sensory-motor deficits, during manipulation they are likely compensating a lack of tactile/perceptual feedback by relying on visual feedback (Bleyenheuft and Gordon, 2013). In case of visuospatial attention deficits, they may present an impaired visual feedback which would lead to deficits in reaching, motor learning and everyday life activities. In this context, rehabilitation of visuospatial attention deficits could be used in children with USCP to reduce their neglect symptoms, improve their motor function as well as their performance in ADL. It is unknown if therapies that are effective interventions for improving visuospatial abilities in adult stroke patients like prism adaptation (Priftis et al., 2013; Rossetti et al., 1998), could have an impact on the visuospatial attention of children with CP.

It is also unknown whether ophthalmological deficits may influence / interfere with visuospatial deficits or whether these impairments are independent. This is of importance since 1) it is estimated that 40 to 90% of the children with CP do have an ophthalmological impairment consisting of strabismus (50%), lower or no stereopsis (60%) and refractive errors (almost 90%) (Fazzi et al., 2012; Kozeis et al., 2007) and 2) the ophthalmological interventions, including surgery, orthoptics exercises, eyes patching, behavioral compensation (Aziz et al., 2006; Collins, 2014; Debert et al., 2016; Dundon et al., 2015; Glisson, 2006) differ greatly from the rehabilitation strategies in case of visuospatial neglect, consisting mainly in stroke patients in limb activation therapy, prismatic adaptation and visual scanning therapy (Luauté et al., 2006b; Priftis et al., 2013).

In children with USCP, to our knowledge no therapeutic intervention has been specifically directed to treating visuospatial deficits. Recently the possibility to induce a transient after effect in children with USCP after one session of prismatic adaptation has been demonstrated (Riquelme et al., 2015). The authors showed that instead of using a pointing task, which is repetitive, and not attractive for children, more ecologic tasks can be used to induce an after effect (Riquelme et al., 2015). However long-term effects/retention of a prismatic adaptation intervention with repetitive sessions on visuospatial deficits have never been demonstrated. Based on the approach demonstrated as efficient in adults with stroke, this might suggested a potential intervention to reduce neglect in children with USCP and improve their independence and performance in ADL.

This thesis aims at answering two questions about visuospatial attention deficits in children with USCP. First: What is the prevalence of ego and allocentric visuospatial attention deficits in children with USCP? Second: Can we treat visuospatial deficits in children with USCP? In addition since ophthalmological deficits are usual in children with cerebral palsy (Cavézian et al., 2012; Fazzi et al., 2012) and may influence results of tests assessing visuospatial attention deficits we investigate in this thesis the potential interaction between ophthalmological impairments and visuospatial attention deficits.

To answer these questions, the present thesis includes four chapters. Chapter II will provide normative values in healthy children for a panel of tests assessing the development of both ego and allocentric visuospatial abilities. Subsequently, in chapter III, visuospatial attention deficits, using the same set of tools, is documented in a large sample of children with USCP. The comparison with normative values provided in the first chapter allows disentangling deficits from physiological age effects. As rehabilitation strategies may differ in visuospatial attention deficits vs ophthalmological impairment, in chapter IV, the potential relationship between both deficits is investigated. Chapter V is dedicated to test whether prismatic adaptation, a rehabilitation strategy shown as efficient in stroke patients presenting a neglect, might be efficient to reduce visuospatial deficits in children with USCP.

Chapter II: Development of visuospatial attention in typically developing children

Aim: The aim of the present study is to investigate the development of visuospatial attention in typically developing children and to propose reference values for children for the following six visuospatial attention tests: star cancellation, Ogden figure, reading test, line bisection, proprioceptive pointing and visuo-proprioceptive pointing.
Method: Data of 159 children attending primary or secondary school in the Fédération Wallonie Bruxelles (Belgium) were collected to the different visuospatial attention tests.
Results: Children's performance on star cancellation, Ogden figure and reading test improved until the age of 13 years, whereas their performance on proprioceptive pointing, visuo-proprioceptive pointing and line bisection was stable with increasing age.
Discussion: These results suggest that the execution of different types of visuospatial attention tasks are not following the same developmental trajectories. This dissociation is strengthened by the lack of correlation observed between tests assessing egocentric and allocentric visuospatial attention, except for the star cancellation test (egocentric) and the Ogden figure copy (ego- and allocentric). Reference values are proposed that may be useful to examine children with clinical disorders of visuospatial attention.

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Introduction

Visuospatial attention is the capacity of someone to attend to and to process stimuli in his surrounding space (Posner and Petersen, 1990). In visuospatial attention, different frames of reference can be distinguished: egocentric or allocentric. The egocentric visuospatial representation is important for movement planning and motor control during direct interaction between body and objects, while the allocentric representation is important for determining spatial references in the environment. The interaction between the allocentric and egocentric visuospatial representations allows for spatial processing.

So far, while the development of attention and visuospatial attention has been investigated in infants and children, few of these assessments are really focusing on defining potential deficits in visuospatial attention (i.e. neglect-like) in ego- and allocentric representations. In egocentric neglect (viewer-centered frame of reference), stimuli presented on one side of the person are neglected while, in allocentric neglect (stimuli/objects centered frame of reference), parts of stimuli/objects are neglected regardless of their location to the person (Medina et al., 2009). Assessments currently used to map the development of visuospatial attention or to establish a diagnosis consist in copies of figures (Rey-Osterrieth figure), cancellation tasks (D2 test), attention tests from neuropsychological batteries (e.g the TEA-Ch and the NEPSY) or are included in IQ test battery as the block design test of the WISC (Manly et al., 2001; Semrud-Clikeman and Ellison, 2007; Stinnett et al., 2002). Besides the use of neuropsychological tests, visual attention and spatial orienting have been investigated in infants and children by using paradigm cueing visual attention to a spatial location. Analyses of eye pursuit and of saccadic movement in several previous studies have also allowed investigating the development of spatial attention (Colombo, 2001; Johnson et al., 1991, 1994; Rueda and Posner, 2013). However, these tests could hardly allow identifying specific ego- or allocentric neglect in children with deficits. As it is hypothesized that spatial cognition develops from an egocentric to an allocentric frame of reference (Piaget and Inhelder, 1948; Piaget, 1937), it seems crucial to have assessments testing and documenting the development of both. Furthermore the possibility to follow the development of a deficit from childhood to adulthood requires the use of similar tools along the whole lifespan. Therefore the aim of this study is to investigate the development of visuospatial attention in typically developing children and to create reference values in six assessment tools often used to diagnose visuospatial neglect in adults: star cancellation, Ogden figure, reading test, line bisection, proprioceptive pointing and visuo-proprioceptive pointing. Specifically, differences in the speed of development were expected between tests assessing egocentric spatial attention and tests assessing allocentric spatial attention as the performance of ego- and allocentric visuospatial attention relies on different neural structures and are likely developing in different time windows.

Among the different tests used in this study, three were previously performed in children. Cancellation tasks using assessments similar to those selected for this study have been previously used to investigate visuospatial attention deficits in children (Katz et al., 1998; Laurent-Vannier et al., 2006). Laurent-Vannier showed that the number of teddy bear omissions decreased with age in typically developing children. Letters or digits cancellation tasks highlighted also a relationship between the test performance and the age of the children (Tharpe et al., 2002; Vakil et al., 2009). Line bisection tests were previously used to measure changes in spatial bias in children (Dobler et al., 2001; Failla et al., 2003; Hausmann et al., 2003; Pulsipher et al., 2009). These studies highlighted an effect of age in the response pattern of the line bisection test as well as in the test performance, older children showing smaller deviations. In addition, Hausmann et al. (2003) showed a potential effect of handedness, with a systematic bias towards the side of the hand used in young children and a change to a bias towards the left side, independently of the hand used, in older children. An effect of handedness has also been observed in copying tasks (Braswell and Rosengren, 2002, 2008), potentially affecting the results of the Ogden copy test. Pointing tasks similar to the one used in this study have been used previously (Hay, 1978), showing an age related performance with a non-linear development demonstrating a maximal error at 7 years old.

As handedness could have an effect on the development and results of the different assessments, a secondary aim of this study is to compare visuospatial attention abilities in left and right -handed children in the different ego- and allocentric tests, with a proportion of left and right handed similar to the general population.

Importantly, one of the tests chosen consists in a copy of a drawing. It is well known that drawing abilities are developing during infancy and childhood. Several previous studies illustrate the development of drawing abilities using notably the Draw-a-Person test (Naglieri, 1988) or the Rey-Osterrieth figure copy (Akshoomoff and Stiles, 1995; Waber and Holmes, 1985). These studies highlighted several drawing developments occurring during childhood such as the development of the drawing planning, which showed improvement between 4 and 10 years old with a change in the strategy of the figure copy (Vinter and Marot, 2007; Vinter et al., 2008). Changes were also highlighted in the use of spatial axes during childhood. Nine and 11-years-old children used spontaneously more often orthogonal and diagonal axes when drawing than 7-years-old children (Lange-Küttner, 2004). Size regulation in drawing, which arises around 5 years, continues to develop during childhood alongside the use of spatial axes. Size regulation development in drawing has been linked to the development of the spatial system and to the use of spatial axes (Lange-Küttner, 1997, 2004, 2008). This development in drawing may influence the performance of children in the copying task. Drawing and copying strategies develop also with age, paralleling the development of writing between 6 and 12 years old which has an influence on the drawing skills (Akshoomoff and Stiles, 1995; Lange-Küttner, 1998; Tabatabaey-Mashadi et al., 2015).

Therefore, the development of drawing will be taken into account in our interpretation of the visuo-spatial test based on a copying task.

Methods

Participants

One hundred and sixty typically developing (TD) children (82 girls, 78 boys, age range: 4.87 to 19.1 yrs, 134 right handed) took part in the study. TD children were recruited from seven French-speaking schools in Belgium (Fédération Wallonie Bruxelles). Schools were selected to vary in the average socio-economic status of their school population and adequately represent the average school-aged population in Belgium. The socio-economic status of each school is described by the SEI index (Socio-Economic Index), a synthetic variable computed on the basis of variables as the mean income per inhabitant, mean household income, educational level, activity level, etc. of the area in which the schools are located (see http://www.fapeo.be/wp-content/analyses/analyses_2011/ISEF.pdf for more information). The selected schools had a mean SEI of 12.6 (4, 13 and 20 for the three primary schools and 10, 11, 14 and 16 for the four secondary schools). SEI values ranges between 1 and 20 with higher values representing a higher socio-economic status. The handedness of each child was determined by writing/drawing hand preference (Waldron and Anton, 1995). Children presenting with central nervous system disease (cerebral palsy, ADHD), vestibular disorder, peripheral neurological lesion of the upper extremity, or any motor or sensory impairment of the upper extremity (as appreciated by the parents) were not eligible for this study. This study was approved by the ethics' committee of the Université catholique de Louvain (Belgian ethics file number: B403201316810). Parents (or legal tutors) and children gave their written informed consent after receiving all information regarding the research protocol.
Participants were selected semi-randomly among the children/parents agreeing to participate and confirming that children did not present an

excluding clinical condition (as described above). This selection was based on gender and age group (need of around 10 children for each age group with a balanced gender ratio). Children were recruited from ages 4 to 19 years old.

Visuospatial assessments

Children were evaluated at school, individually, in a quiet room, while seated on a chair in front of a table adapted to their height. The duration of assessment (time needed to provide instructions and perform all tests) ranged from 10 minutes for the eldest (17+ yrs) to 20 minutes for the youngest children (5-6 yrs). Six assessments were performed in a fixed order: Star cancellation, Ogden figure copy, Reading test, Line bisection, Proprioceptive pointing and visuo-proprioceptive pointing. The children used their dominant hand to perform the different assessments.

Star cancellation

The star cancellation test consists of a page covered with 108 stars (52 big and 56 small) and with distractors (words and letters). The middle of the page is aligned with the subject's midline and the subject is asked to cross out all the small stars. The subject is instructed to put his pencil down as soon as he thinks all small stars are crossed out. Primary variables are the total number of omissions and the time needed to complete the task. For scoring, the page is divided in 4 columns, 1 left (16 small stars), 1 right (16 small stars), 1 center-left (14 small stars) and 1 center-right (10 small stars). The total number of left omissions is the sum of the left column and center-left column omitted stars. The total number of right omissions is the sum of right column and center-right column omitted stars (Wilson et al., 1987). Star cancellation assesses egocentric visuospatial attention as the stars are considered being either on the right or on the left relative to the child (Keller et al., 2005).

Ogden figure copy

Ogden figure copy is a drawing test in which the subject is instructed to copy a drawing. The drawing includes four trees, two on the left and two on the right side of a house located in the middle of the page; the house has a door and four windows (two on the left and two on the right side of the house). The interest of this test is to detect omissions of specific elements in the copy, and not to evaluate the quality of the drawing nor the strategy used by the child during the copy. The test is scored on a scale from 0 to 4, where 0 is a copy without omissions, 1 a copy with omission of a right or left window, 2 a copy with omission of the left or right part of the house or of a tree, 3 a copy with omission of a complete tree and 4 a copy with omission of a complete tree plus another left or right part of the figure. The time needed to complete the task is recorded (Ogden, 1985). Ogden figure copy assesses both ego- and allocentric visuospatial attention (Medina et al., 2009). Omissions of parts of the drawing on the left side or on the right side of the sheet (left or right side relative to the child) are considered as egocentric errors (viewer-based neglect), while omissions of left or right side of the trees or of the house (independently of their position relative to the child) are considered as allocentric errors (stimuli-based neglect). For example, the copy of the house and of only the trees located on the right would be considered an egocentric error, while the copy of the house and of the right part of each tree (trees located on the right and on the left of the house) would be an allocentric error.

Reading test

For the reading test, the subject is instructed to read a text out loud. First-graders and children younger than 7 years old were excluded from this assessment as they lack sufficient reading skills. The text is presented on an A4 sheet of paper in landscape position. The text, written in lower case is composed of 9 lines of text for a total of 77 words. Scoring includes the number of word omissions on either lateral sides of the text, the time taken to read the text, and the number of substitutions on either sides of the text (Reinhart et al., 2013). Both ego- and allocentric errors can be detected by this test (Medina et al., 2009). Omissions of the left or right part of the text are egocentric (viewer-based) errors, while omissions of the left or right part of words independently of their position relative to the child are allocentric (stimuli-based) errors. For example: “longtemps” read as “temps” is an omission of the left part of the word and still an existing word in French, or read as “long” which is an omission of the right part of the word but still an existing word in French.

Line bisection

The line bisection test consists of three pages, each containing ten lines of different lengths to bisect (pages 1: 3 lines of 5cm, 3 lines of 15cm, 2 lines of 20cm and 2 lines of 10cm; page 2: 5 lines of 13.4cm, 3 lines of 9.4cm and 2 lines of 4.7cm; page 3: 3 lines of 2.6cm, 2 lines of 7.9cm, 2 lines of 10.5cm). The subject is instructed to mark the exact middle of each line with a pencil. The percentage error from the line bisection is calculated with the following formula:

Error= (b-a)/a*100

Where a= half of the line length, b the distance between the beginning of the line and the mark made by the child. An error towards the left side of space is recorded as a negative value (Scarisbrick, et al. 1987). Line bisection test assesses allocentric visuospatial attention as children will present a deviation relative to the centre of the line.

Proprioceptive pointing

For proprioceptive pointing the subject is seated in front of a table, his body midline aligned with the center of a paper sheet taped on the table. The sheet of paper is covered with radiating lines indicating the error in degrees from the center of the sheet. Subjects are blindfolded and asked to point towards their perceived body midline on the paper by moving their index finger forward. Each subject performs four pointings. The average value of the four pointings is calculated as the average pointing error. A error towards the left side of space is recorded as a negative value (Riquelme et al., 2015). Proprioceptive pointing assesses egocentric visuospatial attention as the deviation of the pointing will be relative to the body midline of the children.

Visuo-proprioceptive pointing

As described in Riquelme et al. (2015), for visuo-proprioceptive pointing the children are seated in front of a half-open wooden box, closed on one side by a transparent Plexiglas indicating the degrees of error from the center. The base of the box is an isosceles right-angled triangle, with an opening on the hypotenuse side (see Frassinetti et al. (2002) for a complete description of the box). The body midline of the subjects is aligned with the 0° axis of the box (middle of the box). In this position, children are asked to point inside the box (without visual feedback of the range of motion of the arm) towards a target appearing at three different positions above the box. The three different target positions are at 0°, +21° (right side of space) and -21° (left side of space). Each target is presented three times. The mean visuo-proprioceptive pointing error is calculated for each target. The average visuo-proprioceptive pointing error is calculated as the average of all 9 pointings. An error towards the left side of space is recorded as a negative value. Visuo-proprioceptive pointing assesses allocentric visuospatial attention as the deviation of each pointing will be relative to the targets independently of their position.

Statistical analyses

IBM SPSS 22 package was used for statistical analyses. The significance level was set at $p < 0.05$. Descriptive statistics were computed. The normality of distribution and the homogeneity of variances were assessed using Kolmogorov-Smirnov test (normality) and the Levene's test (homogeneity of variance) for each variable in each age group. Tests used to assess handedness, gender and age effects are provided at the start of each result description.

Results

Sample description

From the sample recruited at the start of the study, one child (boy, 4.94 years old, left handed) was discarded of the study because he did not understand instructions and could not complete the assessments. Another child (boy, 4.88 years old, left handed) was unable to perform the visuo-proprioceptive pointing task and therefore a score for this task was lacking for this child. The final sample included one hundred and fifty-nine TD children (82 girls, 77 boys, age range: 4.87 to 19.1 yrs, 134 right handed). Children younger than five years old were included in the age group of 5 years (n=3, age=4.88±0.015). Children older than 17 (n=2, age =18.56±0.761) were included in the 17+ age group. Table 1 is presenting the percentage of left and right handed children per age group.

Age group	Mean age (*SD*)	% left handed (N)	% right handed (N)	N
5	5y2m (3m21d)	22% (2)	78% (7)	9
6	6y5m (3m21d)	27% (3)	73% (8)	11
7	7y6m (3m18d)	14% (2)	86% (12)	14
8	8y6m (3m24d)	8% (1)	92% (11)	12
9	9y7m (2m21d)	7% (1)	93% (13)	14
10	10y5m (3m15d)	15% (2)	85% (11)	13
11	11y4m (4m)	25% (2)	75% (6)	8
12	12y6m (3m18d)	23% (3)	77% (10)	13
13	13y5m (3m3d)	24% (4)	76% (13)	17
14	14y4m (3m)	8% (1)	92% (12)	13
15	15y4m (3m9d)	8% (1)	92% (11)	12
16	16y6m (4m6d)	8% (1)	92% (11)	12
17+	17y7m (6m27d)	18% (2)	82% (9)	11

Table 1: Description of the demographic characteristics and sample size in each age group.

In case of a normal data distribution, outliers > 2.5SD (i.e. SD of this age group) were discarded (considered as an incidental measurement error) and data were expressed as mean and standard error. In case of a non-Gaussian distribution, outliers > 97th percentile were discarded and data expressed as median and percentiles. Following this procedure, solely two subjects tested were considered as outliers for the visuo-proprioceptive pointing and discarded (values of visuo-proprioceptive mean error of +4.88° and +4.77°, respectively at 7 and 9 years old).

The age-related variance of the socio-economic status (as measured by the school SEI) was investigated, using a Kruskal-Wallis test with the factor AGE as between-subjects factor (13 age groups from 5yrs to 17+ yrs). SEI did not differ between the different age groups. Because of the equal distribution of SEI between the different age groups, SEI was not used as a covariate in further analyses (K-W (factor: age-groups): $\chi^2(12, N=159)=10.24; p=.595$).

Visuospatial assessments

One way analysis of variance (ANOVA) with between-subjects factors GENDER (male vs. female) were used in parametric variables to test a potential gender effect. For non-parametric variables, a Kruskal-Wallis test was performed. Gender did not interact significantly with any variable. Therefore the following analyses were performed on the whole sample without splitting boys and girls.

The Age effect was investigated between 13 age groups for all variables. Relative values were created for each assessment and each age group as the 95% confidence interval (mean ± 2SD) for variables with a Gaussian distribution, and as the 95th percentile for variables with a non-Gaussian distribution.

Figures 1A, 2A, 3A and 4-6 show the data distribution per age for each visuospatial assessment. Figures 1B, 2B and 3B show, respectively, the distribution of the variable 'time' for the star cancellation test, Ogden figure copy test and the reading test. The reference values of each visuospatial attention test per age group are described in Appendix

Table 1 A-B for variables with a Gaussian distribution and in Appendix Table 2 A-B for variables with a non-Gaussian distribution.

Star cancellation

Star omission: As the distributions were not Gaussian, handedness was first investigated using a Kruskal-Wallis. An effect of handedness was found for the number of left omitted stars (K-W (factor: right- vs left-handed): $\chi^2(1, N=159)=6.569$; $p=.01$). Left handed children omitted more stars on the left side (number of omitted stars on the left side: right handed: 0.44±0.954; left-handed:1.48±2.275).

An ANOVA on ranks was also performed to investigate age effects. Significant differences between age groups were observed for total star omission, younger children omitting more stars than older children (Figure 1A, Kruskal-Wallis Chi square: $\chi^2(12, N=159) = 56.693$; $p<.001$; post hoc pairwise comparison: 8 yrs vs 14 to 17+ yrs: $p<.042$) as well as for right and left omissions (Kruskal-Wallis Chi square: $\chi^2(12, N=159$ $=39.483$; $p<.001$ and Kruskal-Wallis Chi square: $\chi^2(12, N=159)=50.736$; $p<.001$). In separate analyses made in left handed or right handed children, no age related difference was detected in left handed children for total star omission (Kruskal-Wallis Chi square: $\chi^2(12, N=25)=18.385$; $p=.104$) nor for right and left omission (Kruskal-Wallis Chi square: $\chi^2(12, N=25)=17.308$; $p=.138$ and Kruskal-Wallis Chi square: $\chi^2(12, N=25)=16.743$; $p=.16$). However, the sample size of left-handed children (n=25) was small with on average only two left-handed children per age group. In right handed children, age related difference were highlighted in for total star omission (Kruskal-Wallis Chi square: $\chi^2(12, N=134)=47.294$; $p<.001$) and for right and left omission (Kruskal-Wallis Chi square: $\chi^2(12, N=134)=36.779$; $p<.001$ and Kruskal-Wallis Chi square: $\chi^2(12, N=134)=39.439$; $p<.001$).

Time: Due to a Gaussian distribution and a homogeneity of the variances (Levene's test), handedness was tested using an ANOVA. No effect of

handedness was found (ANOVA (factor: right- vs. left-handed): $F(1,158)=0.670$, $p=.414$).
As a consequence of the difference in the homoscedasticity (Levene's test), an ANOVA on ranks was used to test the effect of age. Significant differences between age groups were observed (Figure 1B, Kruskal-Wallis Chi square: $\chi^2(12, N=159)=97.271$; $p<.001$; post hoc pairwise comparison: 5 yrs vs 12 to 17+ : $p=.002$).

Ogden figure copy

Score: As the distribution was not Gaussian, handedness was first investigated using a Kruskal-Wallis. No effect of handedness was found (K-W (factor: right- vs left-handed): $\chi^2(1, N=159)=0.54$; $p=.815$). A Kruskal-Wallis was also performed to investigate age effects. Significant differences between age groups were observed (Figure 2A, Kruskal-Wallis Chi square: $\chi^2(12, N=159)=52.496$; $p<.001$; post hoc pairwise comparison: 5 yrs vs 6 to 17+ yrs: $p=.013$).

Time: The Gaussian distribution and the homogeneity of the variances (Levene's test) allowed testing handedness using an ANOVA. No effect of handedness was found (ANOVA (factor: right- vs. left-handed): $F(1,158)=0.108$, $p=.743$). As a consequence of the difference in the homoscedasticity (Levene's test), an ANOVA on ranks was used to test the effect of age. Significant differences between age groups were observed (Figure 2B Kruskal-Wallis Chi square: $\chi^2(12, N=159)=96.573$; $p<.001$; post hoc pairwise comparison: 5 yrs vs 12 to 17+ : $p<.001$).

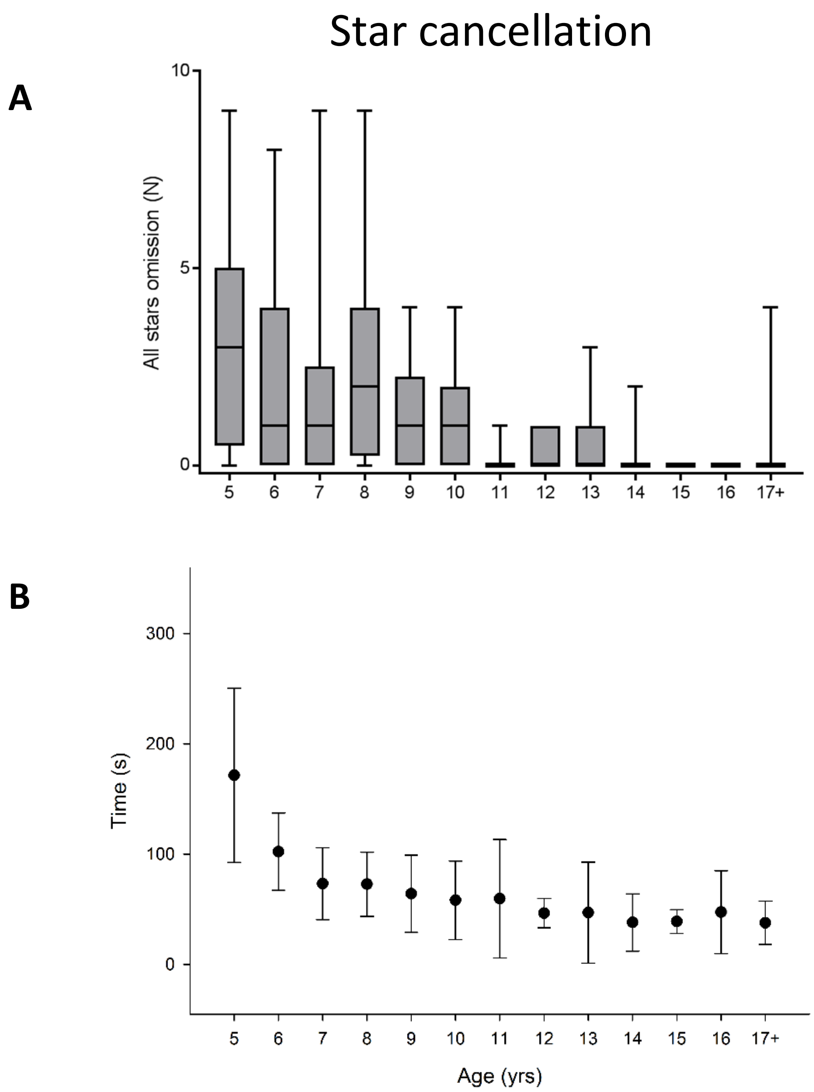

Figure 1: Significant differences between age groups were observed for (A) total star omission (Kruskal-Wallis Chi square: $\chi^2(12, N=159)=56.693$; $p<.001$; post hoc pairwise comparison: 8 yrs vs 14 to 17+ yrs: $p<.042$) as well as for (B) the time taken to complete the test (Kruskal-Wallis Chi square: $\chi^2(12, N=159)=97.271$; $p<.001$; post hoc pairwise comparison: 5 yrs vs 12 to 17+ : $p<.002$).

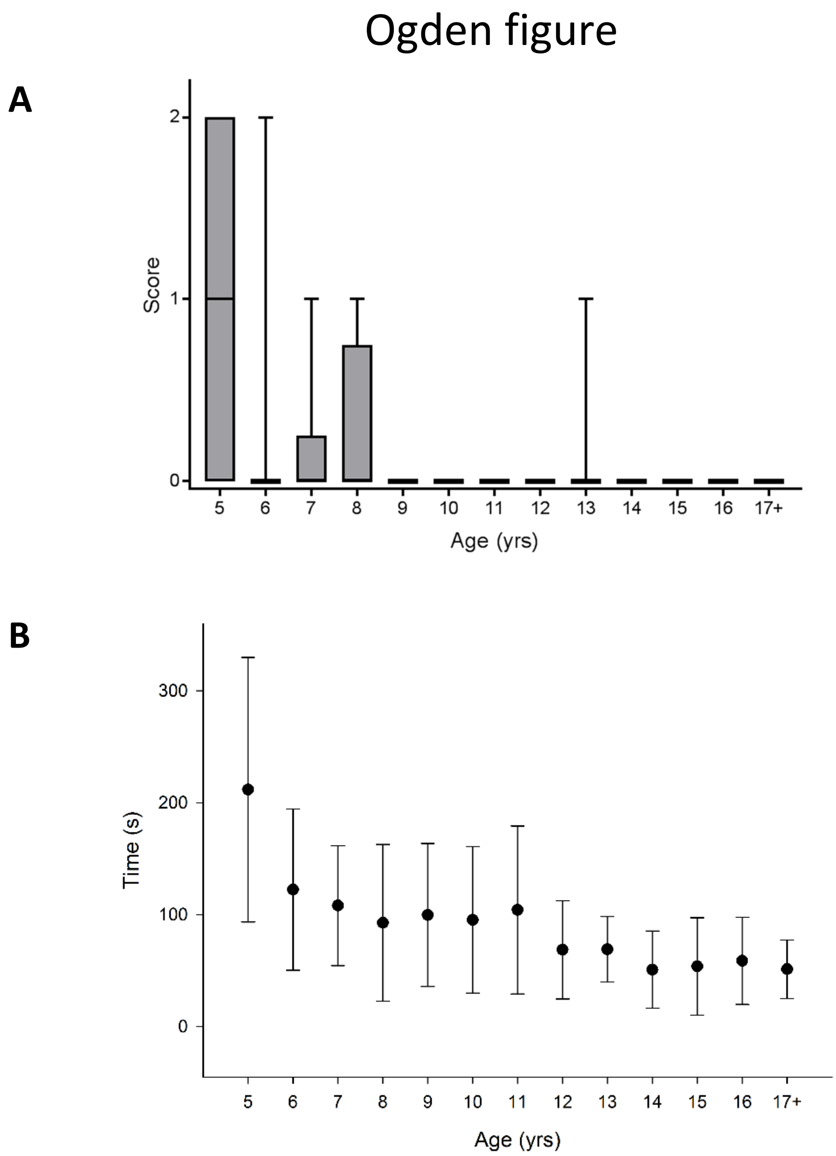

Figure 2: Significant differences between age groups were observed for (A) the Ogden figure score (Kruskal-Wallis Chi square: $\chi^2(12, N=159)=52.496$; $p<.001$; post hoc pairwise comparison: 5 yrs vs 6 to 17+ yrs: $p<.013$) as well as for (B) the time taken to complete the test (Kruskal-Wallis Chi square: $\chi^2(12, N=159)=96.573$; $p<.001$; post hoc pairwise comparison: 5 yrs vs 12 to 17+ : $p<.001$).

Reading test

Word omission: As the distribution was not Gaussian, handedness was first investigated using a Kruskal-Wallis. An effect of handedness was found (K-W (factor: right- vs left-handed): $\chi^2(1, N=134)=4.916$; $p=.027$). A Kruskal-Wallis was also performed to investigate age effects. No age-related difference was observed (Figure 3A, K-W: $\chi^2(10, N=134)=10.072$; $p=.434$) in the whole sample nor in left handed children ($\chi^2(10, N=19)=13.142$; $p=.216$) or in right handed children ($\chi^2(10, N=115)=7.501$; $p=.677$).

Word substitution: As the distribution was not Gaussian, handedness was first investigated using a Kruskal-Wallis. No effect of handedness was found (K-W (factor: right- vs left-handed): $\chi^2(1, N=134)=2.301$; $p=.129$). A Kruskal-Wallis was also performed to investigate age effects. An age-related difference was observed ($\chi^2(10, N=134)=28.692$; $p=.001$; post hoc pairwise comparison: 7 yrs vs 12 to 17+ yrs: $p<.011$).

Reading time: The Gaussian distribution and the homogeneity of the variances (Levene's test) allowed testing handedness using an ANOVA.No effect of handedness was found (ANOVA (factor: right- vs. left-handed): $F(1,133)=0.436$, $p=.510$). As a consequence of the difference in the homoscedasticity (Levene's test), an ANOVA on ranks was used to test the effect of age. An ANOVA on ranks was performed to investigate age effects. Significant differences between age groups were observed (Figure 3 B: Kruskal-Wallis Chi square: $\chi^2(10, N=134)$ 95.065; $p<.001$; post hoc pairwise comparison: 7 yrs vs 12 yrs to 17+ yrs: $p<.001$).

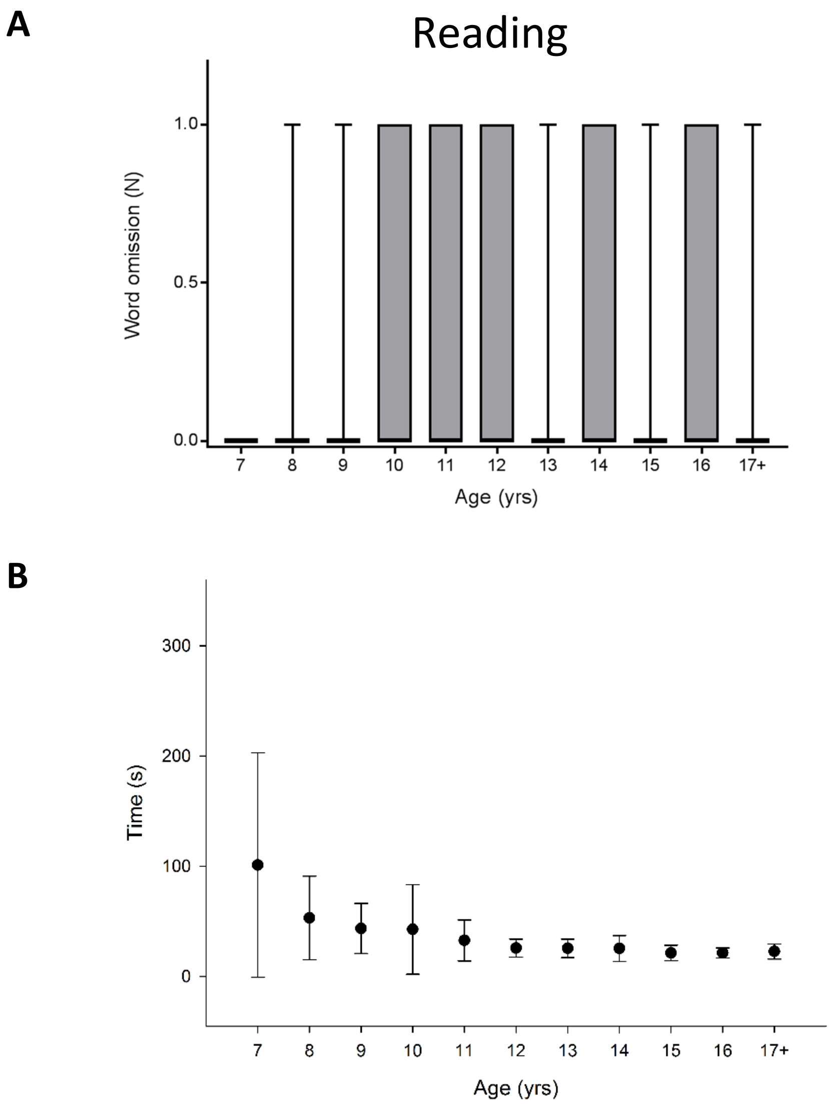

Figure 3: No age related difference was found for (A) the number of omitted word (Kruskal Wallis: $\chi^2(10, N=134)=10.072$; $p=.434$). A significant difference between age groups was observed for (B) the reading time (Kruskal-Wallis Chi square: $\chi^2(10, N=134)=95.065$; $p<.001$; post hoc pairwise comparison: 7 yrs vs 12 yrs to 17+ yrs: $p<.001$).

Line bisection

The Gaussian distribution and the homogeneity of the variances (Levene's test) allowed testing handedness using an ANOVA. An effect of handedness was found (ANOVA (factor: right- vs. left-handed): $F(1,158)=13.994$, $p<.001$). Left-handed children bisected significantly more towards the left side of space than right-handed children (right-handed: -0.71% ±4.117; left-handed: -3.99% ±3.452). Homoscedasticity between age groups was investigated using Levene's test and a difference was found ($F(12;146)=3.134$; $p=.001$). Therefore, Kruskal-Wallis was performed to investigate age effects. There were no age-related differences for line bisection (Figure 4: Kruskal-Wallis Chi square: $\chi^2(12, N=159)=17.566$; $p=.13$). Analyses performed separately in left handed and right handed children, demonstrated no age-related differences for this variable (left handed children: Kruskal-Wallis Chi square: $\chi^2(12, N=25)=11.145$; $p=.517$; right handed children: Kruskal-Wallis Chi square: $\chi^2(12, N=134)=16.689$; $p=.162$). The mean bisection bias of the overall sample was significantly different from zero ($t(158)=-3.698$, $p<.001$) indicating that children bisect significantly away from the midline of peripersonal space towards the left side, the same result was found in left handed and right handed children (left handed: $t(24)=-5.78$, $p<.001$; right handed: $t(133)=-2.001$, $p=.047$).

Complementary investigation: the effect of line length: Effect of line length on bisection error was investigated using One Ways repeated measures ANOVA with the factor line length (4 level: lines of 5cm or less, between 5 and 10 cm, between 10 and 15 cm and line of more than 15 cm) as within subject factor. Analyses showed an overall difference of bisection error between line lengths ($F=7.811$, $p<.001$).

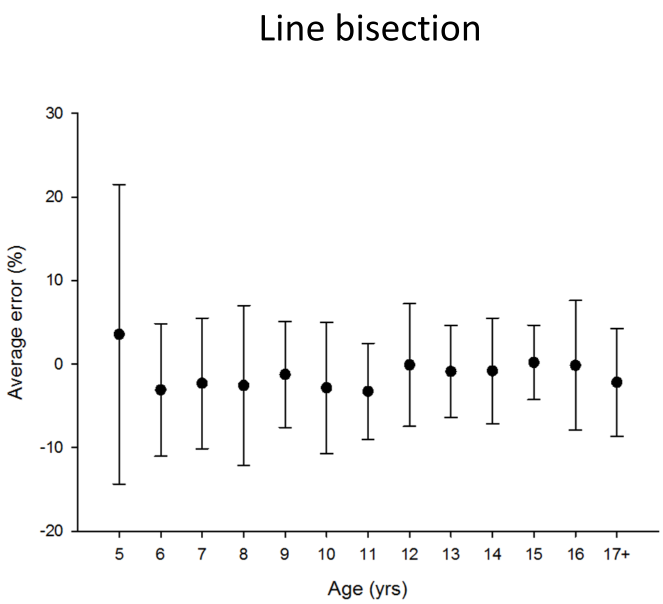

Figure 4: No age related difference was found (Kruskal-Wallis Chi square: $\chi^2(12,N=159)=17.566$; $p=.13$) .

Proprioceptive pointing

The Gaussian distribution and the homogeneity of the variances (Levene's test) allowed testing handedness using an ANOVA. No effect of handedness was found (ANOVA (factor: right- vs. left-handed): $F(1,158)=0.368$, $p=.545$). Difference of variance between age groups was investigated using Levene's test and a difference was found ($F(12;146)=2.526$; $p=.005$). Therefore, a Kruskal-Wallis was performed to investigate age effects. There were no age-related differences for pointing measurements (Figure 5: Kruskal-Wallis Chi square: $\chi^2(12, N=159)=18.866$; $p=.09$). The average proprioceptive pointing of the overall sample was not significantly different from zero ($t(158)=-1.458$, $p=.147$).

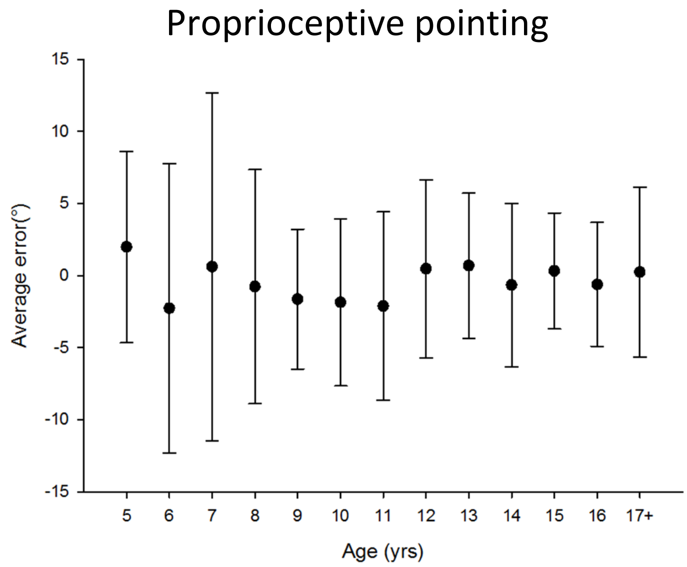

Figure 5 No age related difference was found (Kruskal-Wallis Chi square: $\chi^2(12, N=159)=18.866$; $p=.09$).

Visuo-proprioceptive pointing

The Gaussian distribution and the homogeneity of the variances (Levene's test) allowed testing handedness using an ANOVA. No effect of handedness was found (ANOVA (factor: right- vs. left-handed): $F(1,155)=0.300$, $p=.585$). Difference of variance between age groups was investigated using Levene's test and a difference was found ($F(12;143)=2{,}171$; $p=.016$). Therefore, a Kruskal-Wallis was performed to investigate age effects. There were no age-related differences for pointing measurements (Figure 6: Kruskal-Wallis Chi square: $\chi^2(12, N=156)=14.749$; $p=.255$).

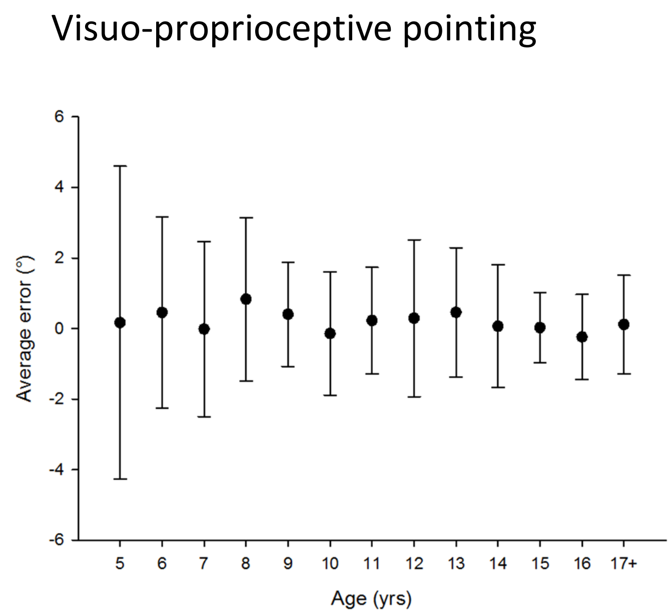

Figure 6: No age related difference was found (Kruskal-Wallis Chi square: $\chi^2(12, N=156)=14.749$; p=.255).

Correlations between visuospatial assessments

Correlations between variables were investigated using Spearman's rank correlation. Correlations were computed on the whole sample as well as for each age group. Level of significance was corrected for multiple comparisons using a Bonferroni correction. Results for the whole sample are displayed in Table 2.

On the whole sample, a significant correlation between the score of the Ogden figure copy test and the total number of omitted stars was observed (r_s=0.256; $p_{corrected}$=.001). No other significant correlation was found in the whole sample (all $p_{corrected}$ >1). Results of Spearman correlations within each age groups did not show significant correlation (all $p_{corrected}$ >*.288*).

	Spearman correlation	1	2	3	4	5	6
1	Star cancellation: All-star omission (n)						
2	Ogden figure copy (score)	.25*					
3	Reading: Word omission (n)	-.02	-.09				
4	Line bisection: Average error (%)	-.15	.03	.02			
5	Proprioceptive pointing: Average error (°)	.00	.13	.04	.07		
6	Visuo-proprioceptive pointing: Average error (°)	.06	-.05	-.11	-.08	-.01	

Table 2: Details of Spearman correlation between visuospatial tests.

Discussion

The present study investigated the development of visuospatial attention in TD children and developed pediatric reference values for both ego- and allocentric visuospatial assessments. Different developmental trajectories were highlighted in test assessing ego- and allocentric visuospatial attention: the line bisection test and the visuo-proprioceptive pointing - the 2 purely allocentric tests - did not show any age-related change. On the other hand, star cancellation, Ogden figure copy and reading tests - either egocentric or ego- and allocentric - presented an age-related development. For assessment tools testing both accuracy and time, a change was observed in both variables. A leftward visuospatial attention bias was observed for the line bisection test.

Differential developmental trajectories in ego- and allocentric tests

The present results do not support our initial hypothesis of children developing first egocentric visuospatial abilities and subsequently allocentric visuospatial abilities. This might be interpreted as a dissociation between spatial cognition and visuospatial attention. In that perspective, egocentric visuo-spatial abilities might develop later since they may depend on self-body representation that is developing through childhood until 10 years old (Brownell et al., 2007; Cowie et al., 2016) while the body per se is changing and the motor control as well as the central representation have to adapt. No age related differences were found in the visuo-proprioceptive pointing task. This is not in agreement with the study of Hay (Hay, 1978), the difference between the studies might be related either to subtle difference between the tasks proposed or the fact that we included more age groups increasing the number of comparisons and potentially decreasing the statistical power.

However, we cannot exclude that the attentional load required by the assessment tools may play a role in the difference observed. Star cancellation is typically considered as measure of sustained and selective attention (Mitrushina et al., 2005), requiring a larger attentional load than line bisection or visuo-proprioceptive pointing. This may interfere since attention function is known to develop with age until 10-11 years old, (Klenberg et al., 2001; Klimkeit et al., 2004).

The difference in the developmental trajectories of ego- and allocentric tests may also be related to different neural substrates underlying the performance of different visuospatial attention tasks (Milner and McIntosh, 2005; Pisella et al., 2013) with egocentric neglect being related to the fronto-parieto-temporal network and allocentric neglect to the parieto-temporal-occipital network (Chechlacz et al., 2010). A difference in the visual stream may also explain different neural substrates underlying both types of visuospatial attention as egocentric neglect appears to be linked predominantly to the dorsal visual pathways while the allocentric neglect may be related to the ventral visual stream (Corbetta and Shulman, 2011; Medina et al., 2009). Egocentric and allocentric visuospatial attention being related to different neural substrates may explain the different rates of development in different visuospatial attention assessments (Loenneker et al., 2011; Pisella et al., 2013). Future functional brain mapping studies (functional magnetic resonance imaging (fMRI) or electroencephalography (EEG)) could clarify the location and development of brain areas involved while performing the visuospatial attention tasks described here.

Developmental trajectories of accuracy

Age differences were highlighted in the development of star cancellation, Ogden figure copy and reading tests. This suggests a development of visuo-spatial attention assessments with an egocentric component that has been previously highlighted. In a teddy-bear cancellation task in children from 3 to 8 years old, Laurent-Vannier et al. (2006) showed that typically developing children presented more teddy bear omissions before 6 years old than after. This development towards a better performance at 6 years old is congruent with our data and closely matches the time results observed in our star cancellation results and the development of our scores at the Ogden figure. The development observed in the Ogden figure copy is in line with previous studies using the copy of a complex figure, the Rey-Osterrieth figure, where children at the age of 6 omit almost no elements of the figure and improve until the age of 9 (Akshoomoff and Stiles, 1995; Waber and Holmes, 1985). Finally in the present study, the development in reading omissions is observed later since the test per se is not proposed under the age of 7.

Other factors than visuospatial attention could have influenced the changes observed in these results. The socio-economic status, for instance, may have had an influence. However, in the present study SEI was equally distributed among the different age groups and could therefore not explain the age effect observed. Some other non-visuospatial factors may have potentially influenced the results of the present study, such as the development of drawing and perception of object size (Akshoomoff and Stiles, 1995; Bremner, et al., 2000; Lange-Küttner, 2008; Vinter and Marot, 2007; Vinter, et al., 2008; Waber and Holmes, 1985). In the Ogden figure copy, our results closely match the development of some drawing abilities. Several authors reported a transition in drawing development around the age of 5-6 years old. Children around 5 years old start regulating the size of different objects drawn together (Lange-Küttner, 2008). Around the same age children

change the way they plan their figure drawing, driven by the figure characteristics and no more by a left to right progression (Vinter et al., 2008). The difference observed in the Ogden figure copy between 5 and 6-years-old children could in part reflect the general development of drawing abilities in children and not only the development of visuospatial abilities. Though the development of drawing abilities may in part explain the changes observed in the Ogden figure copy, they are not likely to influence the other egocentric assessments – i.e. not including drawing.
The star cancellation test may have been influenced by the ability of children to distinguish big stars from small stars. Previous studies reported that children at the age of five understand the concept of big and small and are able to distinguish a big object from a small one while the objects are simultaneously presented (Gelman and Ebeling, 1989; Smith, et al., 1985). Therefore, our results showing a development in the score of star cancellation are probably more related to visuo-spatial attention than to the concept of object size.

A correlation was observed between scores (accuracy) in the Ogden figure copy and the total number of omitted stars. This correlation can be explained by the concomitant age-related changes in both tests and by the fact they both assess a combination of ego- and allocentric visuospatial attention.

Developmental trajectories of time taken to perform the tasks

This study showed that the time needed to perform the star cancellation, the Ogden figure copy and the reading test decreases until the age of 12 years old. These results highlight a dissociation between the development of the time needed to perform the tasks and the performance/accuracy in the different tasks. This seems crucial to take into account when using these tests as assessments tools in children with potential deficits of visuospatial attention. Such a dissociation between speed and accuracy while performing a complex motor task have been previously described by Reis et al. (2009) who described the development of the relationship between these two parameters as the key element for inducing a skilled motor learning. At least regarding the Figure copy, the task required by the children might be considered as a complex motor task. Though the accuracy is maximal quite early, an improvement in performance is still possible through the change in the time needed to perform the task. Concerning the time needed to carry out the Ogden figure copy, Lange-Küttner highlighted in a previous study (1998) that 6-years-old children are copying angular shape more efficiently than the 4-year-olds. In comparison to younger children, older children were faster when copying angular forms than round forms. The authors suggested that these results could partially be explained by the geometric perfection of round forms in older children in comparison to the ubiquitous round forms in the drawings of younger children. Indeed a development of the time taken to copy the figure can be observed graphically (Figure 2). The age where a stabilization in the time needed to complete the copy is observed in our data – 12 years old -matches in Belgium the start of secondary school (second cycle). The larger amount of exposure taking notes during classes at this age may represent a potential bias and may play a part in the reduction of time needed to carry out the tests between 11 and 12 years old.

Developmental trajectories of spatial bias

The present data show a leftwards pointing bias in the line bisection test, regardless of age. This leftwards bias has been described previously in healthy adults when performing line bisection tasks and pointing tasks (Jewell and McCourt, 2000; Richard, et al. 2004). The leftwards bias found in healthy adults may be related to the attentional dominance of the right posterior parietal lobe, which is a critical region for performing the line bisection task in the near space (Bjoertomt et al., 2002; Chechlacz et al., 2012a). There is some controversy regarding the presence of leftwards visuospatial bias in children when using the line bisection test (Bowers and Heilman, 1980). Studies in young children have shown a bias in function of the hand side used for performing the line bisection task (Hausmann, et al. 2003; Failla, et al. 2003; Dobler et al. 2001). In the present study, children were instructed to use their dominant hand only. Differences were found for line bisection according to the handedness, which is congruent with previous results by Pulsipher et al (2009) reporting both leftwards and rightwards biases for line bisection in TD children. These biases seem to develop after 4 months of age since Lange-Küttner and Crichton (1999) showed that young infants present a bias of attention towards the right side of their visual field, which is comparable to neglect in adult patients. However, this attention bias resolves itself during the 4th month of life with the apparition of reaching in which infants show preference for reaching objects in their left visual field (Lange-Küttner and Crichton, 1999). At the same age previous studies reported that children can direct their gaze, engage and disengage their attention as well as shift it (Colombo, 2001).

Limitations

A recruitment bias cannot be excluded as it was impossible to distinguish between parents whose children presented an exclusion criterion and parents who didn't agree to let their child participate. Also, the present reference values were collected in a school-aged pediatric population in Belgium and may differ according to ethnical and/or cultural origins.

Assessments were carried out in a fixed order. This procedure may have induced a bias due to fatigue. However, in the present study, the total time of testing was short and each task separately did not last more than 2 minutes. The visuospatial attention assessments were presented as games to the children. Though it seems unlikely that the fixed order of assessments may have induced fatigue, this possibility cannot be ruled out. Concerning the results of the reading text, as the text was written in lower case, younger children may have encountered more difficulties to read it. The measure of time could have been biased by some children trying to do the tests as fast as possible. Children were not asked to hurry during the tests, however, they knew that the time was being recorded which might be understand by some as a signal to do the test as fast as possible.

Conclusion

The present study describes pediatric reference values for visuospatial attention assessments and the development of visuospatial attention with age. Reference values are useful to detect visuospatial attention deficits in function of age and to describe pathological results. The use of visuospatial attention tests that are commonly applied in adults allows for an easy follow-up of visuospatial attention deficits during the transition from childhood to adulthood. Differential effects of age were observed with regards to the developmental trajectories of the different visuospatial assessments. Different neural substrates underlying different types of visuospatial attention (egocentric vs. allocentric) may explain differences of developmental speeds between visuospatial attention assessments.

Chapter III: Impairments of Visuospatial Attention in Children with Unilateral Spastic Cerebral Palsy

Aim: The aim of this observational study was to assess the prevalence of visuospatial attention deficits in children with unilateral spastic cerebral palsy (USCP), taking into consideration the affected hemibody.
Method: Seventy-five children with USCP were assessed with four visuospatial attention tests: star cancellation, Ogden figure copy, line bisection, proprioceptive pointing.
Results: A majority (64%) of children with USCP presented a deficit in at least one test compared to the reference values. The alterations observed in children with left or right USCP were related to egocentric or allocentric neglect, respectively. Children with cortico/subcortical lesion presented more often visuospatial attention deficits than children with periventricular lesion.
Interpretation: Visuospatial attention deficits are prevalent in children with USCP and should be taken into account during their rehabilitation process. The present results shed new light on the interpretation of motor impairments in children with USCP as they may be influenced by the frequent presence of visuospatial deficits.

Submitted as: Ickx, G., Hatem, S. M., Riquelme I., Henne C., Araneda R., Gordon A. M. and Bleyenheuft, Y.. Impairments of Visuospatial Attention in Children with Unilateral Spastic Cerebral Palsy, in *Neural Plasticity*

Introduction

Cerebral Palsy (CP) is present in 2 to 3.6 out of thousand live births and results from brain lesions occurring during prenatal, perinatal or early postnatal life. One of the most common subtypes of CP is unilateral spastic cerebral palsy (USCP) which represents up to 34% of all cases (Pakula et al., 2009; Shevell et al., 2009; Wichers et al., 2005; Yeargin-Allsopp et al., 2008). The main consequence of USCP is motor impairment which depends on the timing, size and localization of the lesion as well as on the child's cerebral reorganization and recovery (Mailleux et al., 2017). Additional impairments include deficits in sensory and cognitive function as well as sensory-motor integration (Bleyenheuft and Gordon, 2013; Straub and Obrzut, 2009). Visuospatial attention is the capacity of someone to attend to and to process stimuli in his surrounding space (Posner and Petersen, 1990). Visuospatial attention deficits are likely to be present in children with USCP, probably at least in part, influenced by the impact of the motor deficit over the attentional system (Smith and Chatterjee, 2008), though they scarcely have been studied.

Visuospatial attention deficits have been widely studied in adult patients with acquired brain lesions and are mainly observed in lesions of the right hemisphere. They lead to hemineglect of the contralesional body and hemispace in 10 to 33% of patients (Chechlacz et al., 2012b; Hillis, 2005; Kleinman et al., 2007). Neuroimaging studies have shown a relationship between hemineglect and lesions located in the right temporo-parietal junction (TPJ), as well as in certain areas of the frontal, parietal and temporal lobe (Chechlacz et al., 2012a; Corbetta and Shulman, 2011). In visuospatial attention, different frames of reference – either egocentric or allocentric - can be distinguished. Egocentric neglect is described with regards to the body midline of the patient (i.e. the patient neglects stimuli presented on one side of the hemispace referred to his own body midline) and allocentric neglect is described with regards to the midline of an object in the peripersonal or extrapersonal space (i.e. the patient neglects stimuli on one side of the object's midline).

Few studies have reported visuospatial attention deficits related with visuospatial neglect in children with early brain lesions. Trauner (Trauner, 2003), in a study with a large sample of children with early brain lesions (n=60) and typically developing (n=36) children, reported evidence of spatial neglect in two-thirds of children with both left and right brain lesions. In this study, a board with toys was presented to toddlers and the localization of toys touched by the child was recorded. Others studies (Katz et al., 1998; Laurent-Vannier et al., 2003; Thareja et al., 2012) also reported the presence of spatial neglect in children with a right or left early brain lesion using, for example, the teddy bear cancellation test. Another study focused on children with early left brain damage (Lidzba et al., 2006) and reported the presence of a correlation between the reorganization of language function in the right hemisphere and visuospatial performance in the star cancellation test. These studies showed visuospatial attentional deficits in children with right or with left brain lesion contrasting with deficits acquired in adult brain lesion that mainly are associated with right cerebral lesions. This suggests differences in the distribution of visuospatial abilities between the developing and mature brain.

The egocentric visuospatial representation is important for movement planning and motor control during direct interaction between body and objects, while the allocentric representation is important for determining spatial references in the environment. The interaction between the allocentric and egocentric visuospatial representations allows for spatial processing (Burgess, 2006; Colby, 1998). While both allocentric and egocentric representation show a progressive maturation with age in typically developing children, solely egocentric representation reaches maturity upon adolescence (Campanella et al., 2011; Tinelli et al., 2017). Despite the relevance of both spatial representations, most of the studies in children with USCP have used tools to study egocentric neglect (cancellation tasks, figure copy and drawing). None of the previous studies assessed allocentric neglect in a large sample of children with USCP (Keller et al., 2005).

The aim of the present study is to investigate the prevalence of visuospatial attention deficits in a large sample of children with USCP, using both ego- and allocentric tests with regards to the affected hemibody. We hypothesized that many children with USCP would show abnormal values in both ego- and allocentric visuospatial attention tests. Detecting the presence of these deficits appears as important to tailor the rehabilitation process to each child and thus to improve his/her ability in everyday motor activities.

Methods

Participants:

Children with USCP were recruited and assessed during intensive rehabilitation interventions organised by the MSL-IN Lab (Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium) and the Center for Cerebral Palsy research (Columbia University (CE) Teachers College, United States) during four consecutive years (2012-2015).

Children were classified following the Manual Ability Classification System (Eliasson et al., 2006) as levels I (n=16), II (n=50) or III (n=9). In addition, when MRI was available brain lesions were classified by a neuroradiologist using the criteria of Krägeloh-Mann and Horber (Krageloh-Mann & Horber, 2007), allowing to define the origin/timing of their brain lesion (cortical malformation, n=6; periventricular lesion, n=31; cortical/subcortical lesion, n=32). Details of the demographic and clinical data are summarized in Table 1.

Table 1: Demographic and clinical characteristics of children

General Characteristics		More affected upper extremity		
		Left	Right	All
Age		9y5m (3y)	9y1m (2y11m)	9y3m (2y11m)
Gender (N)	female	9	24	33
	male	21	21	42
Lesion Timing (N)	Brain malformation	4	2	6
	Periventricular white matter lesion	14	17	31
	Cortical/subcortical lesion	10	22	32
	NA	2	4	6
MACS (level)	Level I	7	9	16
	Level II	22	28	50
	Level III	1	8	9
Total (N)		30	45	75

MACS= Manual Ability Classification System

Consistent with previous intensive interventions of these teams (Bleyenheuft et al., 2015; Gordon et al., 2007), inclusion criteria were: 1) aged between 5 and 18 years, 2) ability to grasp light objects and lift the more affected arm 15 cm above a table surface, 3) ability to follow instructions and complete testing. Exclusion criteria were: 1) uncontrolled seizures, 2) orthopedic surgery or botulinum toxin injections less than twelve months before or within the study period, 3) possibility of treatment/testing interference because of visual problems (i.e because thorough ophthalmological data were not available, this exclusion criterion was based on a statement made by the practitioner following the child). Participants and caregivers provided informed consent. The study was approved by the Institutional Review Boards of the Teachers College Columbia University and of the Université Catholique de Louvain.

Assessment Tools:
Children had to perform 4 visuospatial attention tests currently used in adult patients and for which reference values are available in typically developing children of the same age (Ickx et al. 2017).

Star cancellation: The test consists of an A4 sheet of paper with stars of two different sizes as well as distractor words which are semi-randomly distributed. The child is asked to cancel all small stars. The following variables are recorded: the number of stars omitted on each side (left, right) and the total number of omitted stars (Wilson et al., 1987). The absolute difference between the number of left omitted stars and right omitted stars also is computed. The variable used to determine if a child with USCP presents with an abnormal value compared to reference values is the total number of omitted stars. Star cancellation mainly assesses egocentric neglect(Keller et al., 2005).

Ogden figure copy: This test consists of a drawing copy task. The child is asked to copy a figure (a house and 4 trees). The score ranges from 0 (no omissions) to 4 (multiple omissions) (Ogden, 1985) and is the variable used to determine if a child with USCP presents with an abnormal value compared to reference values. Ogden figure copy assesses both ego-and allocentric neglect (Medina et al., 2009).

Line bisection: The line bisection test consists of 2 pages with 10 lines of different lengths on each page. The child is asked to indicate the middle of each line by making a mark with a pencil. The deviation from the centre, in percentage of half the line length, is computed with the following formula:
deviation= (b-a)/a*100
where a= half length of the line and b = distance between the beginning of the line and the mark made by the child (Scarisbrick et al., 1987). The variable used to determine if a child with USCP presents with an abnormal value compared to reference values is the average deviation

(in percentage) from the centre of each line. Line bisection test assesses allocentric neglect. An error towards the paretic side of space is recorded as a negative value.

Proprioceptive pointing: The child is blindfolded and seated in front of a table. A paper sheet with angled graduation lines (deviation in degrees) from a central point is aligned with the body midline of the child. The child is asked to point straight ahead on the table by moving his finger (Riquelme et al., 2015). The pointing is performed three times. The variable recorded is the average deviation (mean of the three pointings in degrees) with regards to the child's body midline. This variable is used to determine if a child with USCP presents with an abnormal value compared to reference values. Proprioceptive pointing assesses egocentric neglect. A deviation towards the paretic side of space is recorded as a negative value.

Statistical analysis:

Descriptive statistics: A child with USCP was considered to have an abnormal value for any of the visuospatial attention tests if his/her result was outside the age-corrected reference values published previously (Ickx et al. 2017).

Chi-Square tests were used to compare the prevalence of abnormal test values between children with left USCP and children with right USCP as well as between children with predominant periventricular brain lesions and children with cortico/subcortical brain lesions. Student t-test was used to compare intra-subject differences between omissions on one side and the other side of hemispace for the star cancellation test. The statistical analysis package SPSS was used for all analyses. Significance level was set at $p \leq 0.05$.

Results

Prevalence of visuospatial attention deficits in children with USCP:

The sample consisted of 75 children with USCP from 5 to 17 years old (mean= 9y3m, *SD*=2y11m, 42 boys and 33 girls): 45 children with right USCP and 30 children with left USCP. Sixty percent of the children presented with abnormal values in at least one visuospatial attention test. 28% of the children with USCP presented with abnormal values in two or more visuospatial attention tests. 10.7% of the children presented with abnormal values in three or more visuospatial attention tests. Differences in the percentage of children with deficits were detected depending on the timing of the lesion: compared to children with periventricular lesions, a larger percentage of children with cortico-subcortical lesions presented visuospatial attention deficits (χ^2(3, n=32)=16.655; *p*=0.001). Figure 1 shows the prevalence of abnormal values for one, two, three or more tests in the whole sample of children with USCP as well as in children classified by lesion timing.

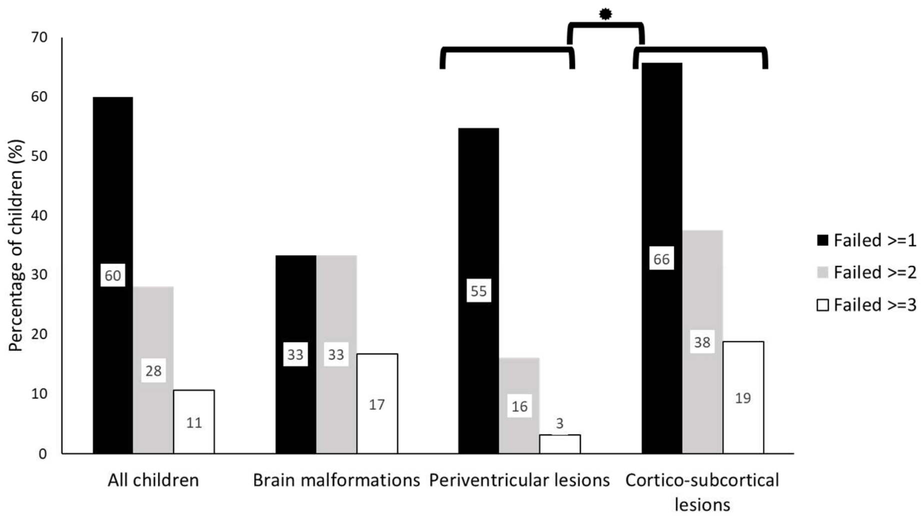

Figure 1: Percentage of children presenting with a visuospatial attention deficit in the whole sample

Prevalence of abnormal findings in each of the visuospatial attention tests in children with USCP:

The prevalence of abnormal values in each of the four visuospatial attention tests in children with USCP, is described in Figure 2 and 3.

Star cancellation: 18.7% of the children (number of tested children = 75) presented with abnormal values. The absolute difference between left and right omitted stars was significantly different from 'zero', indicating that children omitted more stars on one side than on the other (children with left USCP: $t(1, 29)$=2.769; p=0.01; children with right USCP: $t(1, 44)$=4.100; p<0.0001) (Figure 3). When the prevalence of abnormal values was compared between children with left and right USCP, children with a left USCP presented significantly more abnormal values for left omitted stars than children with right USCP (χ^2(1, n=30)=4.559; p=0.033) (Figure 4). The prevalence of abnormal values was not significantly different between children with periventricular or cortico-subcortical lesion for the total number of omitted stars: χ^2(1, n=32)= 2.294; p=0.130). In the number of **right** omitted stars, the prevalence of abnormal values was significantly larger in children with cortico-subcortical lesions than in children with periventricular lesions (χ^2(1, n=32)=49.095; p<0.001).

Ogden figure copy: 25.3% of the children (number of tested children = 75) presented with abnormal values. The prevalence of abnormal values was not significantly different between children with right and left USCP: χ^2(1, n=30)= 0.084; p=0.773). The prevalence of abnormal values was significantly higher in children with cortico-subcortical lesions than in children with periventricular lesions (χ^2(1, n=32)=9.590; p=0.002) (Figure 3).

Line bisection: 44% of children (number of tested children =75) presented with abnormal values. Twenty-five children were above the upper bound of the reference range (i.e. bisection deviated towards the non-paretic hemispace) and 8 children were below the lower bound of the reference range (i.e. bisection deviated towards the paretic hemispace). Children with right USCP had abnormal values more often than children with left USCP (χ^2(1, n=45)6.427; *p*=0.011; children with right USCP = 51.1% and children with left USCP = 33.3%). In the line bisection test, the prevalence of abnormal values was not significantly different in function of lesion timing (χ^2(1, n=32)= 2.807; *p*=0.094).

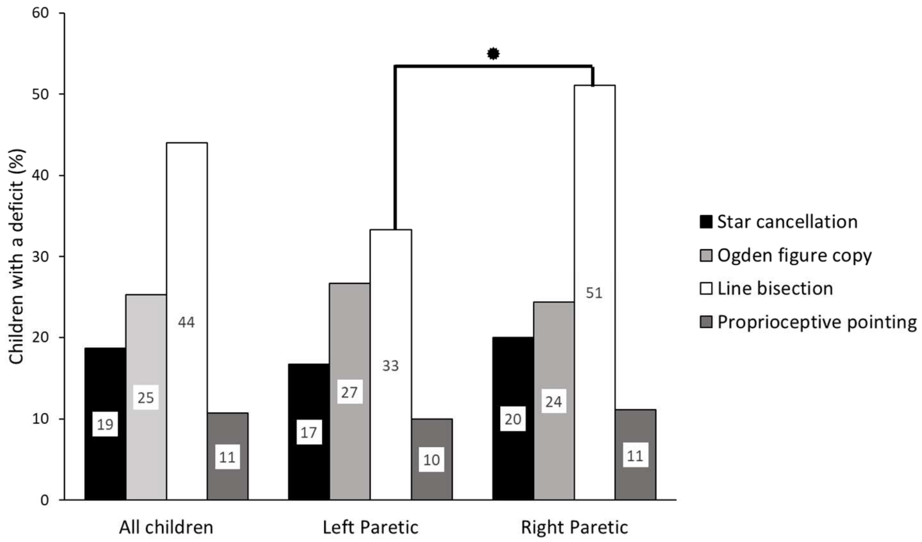

Figure 2: Percentage of children with USCP with abnormal values in each visuospatial attention test for the whole sample and for children with left or right USCP. Chi-square *p<0.05

Proprioceptive pointing: 10.6% of children (number of tested children = 75) presented with abnormal values: 7 children deviated towards the non-paretic hemispace and 1 child deviated towards the paretic hemispace. The prevalence of abnormal values was not significantly different between children with right and left USCP: χ^2 (1, n=30)= 0.037; *p*=0.848). The prevalence of abnormal values was not significantly different between children with predominant white matter lesions and predominant grey matter lesions: χ^2 (1, n=32)= 1,283; *p*=0.257).

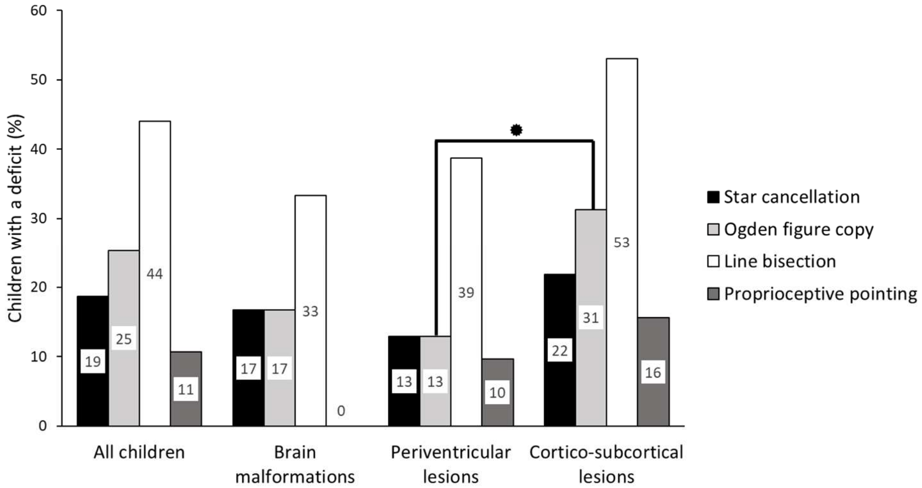

Figure 3: Percentage of children with USCP with abnormal values in each visuospatial attention test for the whole sample and for children with brain malformation, periventricular lesion, or cortico-subcortical lesions. Chi-square *p<0.05

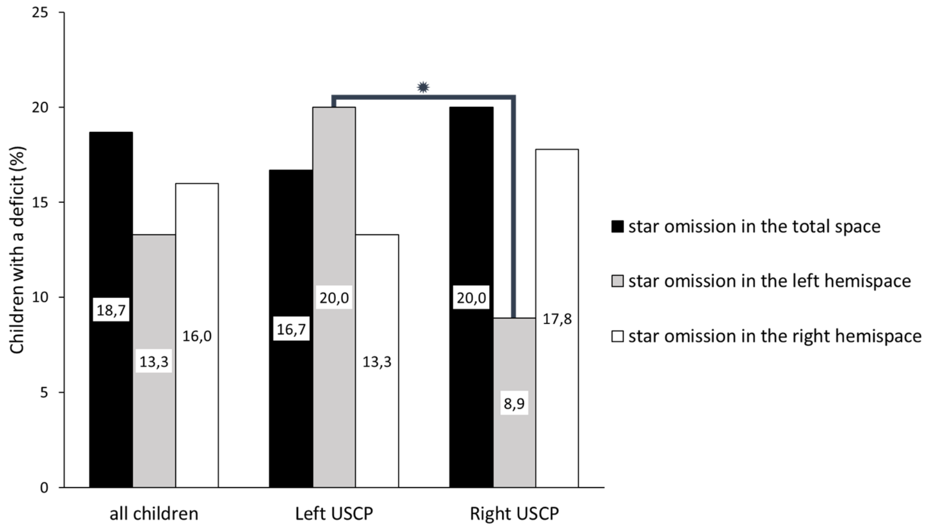

Figure 4: Percentage of children with USCP with abnormal findings in the star cancellation test for each hemispace (star omission in the total space, star omission in the left hemispace, star omission in the right hemispace). Chi-square *p<0.05

Discussion

The aim of this study was to investigate the prevalence of visuospatial attention deficits among children with USCP using both ego and allocentric tests, taking into consideration the affected hemibody. A majority of children with USCP presented with abnormal visuospatial attention as 60% of our sample scored outside the reference values for at least one visuospatial attention test. In addition, the results indicated a difference between children with left and right USCP. Children with a left USCP showed predominantly an egocentric impairment and children with a right USCP showed mainly an allocentric deficit. Lesion timing also had an influence on the prevalence of visuospatial attention deficits: children with cortico-subcortical lesions presented more frequently visuospatial attention deficits than children with periventricular brain lesion.

More than half of the children participating in this study presented with abnormal values for at least one visuospatial attention test and almost one third of the sample for two or more tests. The high prevalence of visuospatial attention deficits among children with an early brain lesion has been reported in previous studies (Katz et al., 1998; Laurent-Vannier et al., 2003; Thareja et al., 2012; Trauner, 2003). The presence of visuospatial attention deficits and in particular neglect of one side of space could be relevant for the rehabilitation process in children with USCP. The evidence shows that visuospatial attention interacts with motor function, for instance, during eye-limb coordination (Smith and Chatterjee, 2008). In this way, an early motor deficit could have an impact on the development of the attentional system (Chatterjee, 2002), for example children with spastic diplegia have shown impairments in visual orientation tasks (Craft et al., 1994).

Visuospatial attention deficits were more frequently observed in children with cortico-subcortical lesions than in children with periventricular lesions. Previous studies suggested that children with cortico/subcortical lesion generally present with larger lesions than children with periventricular lesions. Also in these children, more associations are observed between lesions characteristics and clinical outcomes (Feys et al., 2010; Mailleux et al., 2017). Maillieux et al. (Mailleux et al., 2017) reported frequent and stronger associations between lesions characteristics (size, localization, extent) and motor function in children with cortico/subcortical lesion than in children with periventricular lesions. Impaired upper extremity function (Feys et al., 2010) and language skills (Coleman et al., 2013) are also more common in CP children with cortical/subcortical compared to periventricular lesions. This overall larger prevalence of deficits in children with cortico/subcortical lesions could be explained by the timing of the lesion. Cortico/subcortical lesions typically arise at the end of the 3rd trimester of gestation (Krägeloh-Mann and Horber, 2007): the later the lesion, the less likely it may allow for efficient reorganization/rewiring of affected functions in the brain.

In our results, we observed alterations of visuospatial attention in children with right as well as left brain lesions, which differs from previous observations in adults demonstrating mainly hemineglect with right brain lesions (Bowen et al., 1999) due to the lateralization of visuospatial abilities within the right hemisphere (Corballis, 2003). The fact that left brain lesions can lead to an alteration of visuospatial abilities in children with USCP can be explained by the important cerebral reorganization occurring after an early brain lesion. This observation may be explained by the "crowding hypothesis" (Anderson et al., 2011; Lidzba et al., 2006): a left hemispheric lesion can shift the areas related with language from the left to the right hemisphere, affecting thus visuospatial function. Liszba et al. (Lidzba et al., 2006) highlighted a correlation between the reorganization of language function in the right hemisphere and visuospatial performance in children with early cerebral lesions.

Differences in the type of hemineglect were observed between children with left and right USCP. In the star cancellation test (assessing mainly egocentric neglect), children with left USCP omitted more stars on the left side than on the right side and were more often outside the normative values for the number of left omitted stars than children with right USCP. On the other hand, children with right USCP more frequently presented with abnormal values of the line bisection test compared to children with left USCP, suggesting more often allocentric visuospatial impairment (Keller et al., 2005). It has been suggested that different brain substrates are linked to egocentric and allocentric neglect: egocentric neglect being linked to the fronto-parieto-temporal network, while allocentric neglect being related to the parieto-temporo-occipital network (Chechlacz et al., 2010). Specifically, egocentric representation has been related with activation in the medial part of the left superior parietal lobe, and the allocentric representation with an activation in the right parietal lobe, occipito-temporal cortex and hippocampal regions (Zaehle et al., 2007). Besides the side of hemispheric lesion, specific characteristics of the brain lesion, post-lesional brain reorganization and development also may explain the differential visuospatial attentional impairments: larger brain lesions have been observed in children with right USCP than in children with left USCP (Scheck et al., 2014, 2016). Regarding brain reorganization and development, children with left USCP are more likely to present visuospatial attention deficits that are directly related to the location and size of the lesion in the right hemisphere. One of the limitations of the present study is the lack of detailed characterization of the size and location of the brain lesion. Future studies should include medical imaging in combination with visuospatial and other neuropsychological assessments. Future studies also should include an ophthalmological examination to exclude underlying anatomical impairments of vision as a substrate for visuospatial attention deficits.

This study gives a better insight in the prevalence of visuospatial attention deficits in children with USCP and highlights that visuospatial deficits are common among children with USCP and more frequent in children with cortico/subcortical lesions than in children with periventricular lesions. In order to properly diagnose these deficits, both egocentric and allocentric visuospatial attention tests are needed. Children with right and left USCP do not present the same type of visuospatial attention deficits: left USCP is more linked to egocentric neglect while right USCP is more linked to allocentric neglect. The present findings may help improving the rehabilitation of children with USCP as visuospatial abilities are critical for motor skill learning and motor control. Depending on the side of the brain lesion, children may show differential responses related to the lateralization aspect of these deficits. Different rehabilitation interventions have been described in adult patients such as vestibular stimulation or prismatic rehabilitation (Jacquin-Courtois et al., 2013; Sturt and David Punt, 2013; Wilkinson et al., 2014). Prismatic rehabilitation has been reported as feasible in children with USCP (Riquelme et al., 2015). Future studies should therefore investigate the effectiveness of prismatic rehabilitation applied to children with USCP for improving visuospatial neglect and possibly motor skill learning.

Chapter IV: Visuospatial attention deficits and ophthalmological impairments in children with unilateral spastic cerebral palsy

Background: Previous studies reported the presence of visuospatial attention deficits in around fifty percent of children with unilateral spastic cerebral palsy (USCP). Visuospatial assessments can be influenced by ophthalmological impairments. Ophthalmological impairments have been reported for a long time in children with cerebral palsy (CP), with around fifty percent of the children with USCP presenting binocular vision impairments and strabismus. Thus, it seems important to disentangle the relationship between the two.

Methods: A sample of 15 children with USCP between 5 and 17 years old was recruited and assessed for both ego- and allocentric visuospatial attention deficits, with a battery of paper and pencil tests used previously in children with USCP, as well as for ophthalmological impairments with a standard examination (visual function, binocular vision, ophthalmological health). Relationship between the two kinds of deficits was investigated using Spearman's correlations and Fisher's exact tests.

Results: A significant correlation solely was highlighted between the proprioceptive pointing test (visuospatial attention test) and strabismus; impaired stereopsis and visual field defects were found. No associations between visuospatial and ophthalmological deficits were highlighted by the Fisher's exact test.

Conclusion: According to these results, visuospatial attention deficits do not seem to be associated with ophthalmological deficits. The significant correlations seem to indicate an impaired internal body representation rather than an association between lateralized visuospatial deficits and ophthalmological deficits.

Introduction

Cerebral palsy (CP), resulting of an early brain lesion occurring during prenatal, perinatal or early postnatal life, is present in 2 to 3.6 per thousand live births and is characterized by a motor impairment (Pakula et al., 2009; Yeargin-Allsopp et al., 2008). The motor impairment and cerebral palsy subtype depend on the timing, size and localization of the brain lesion (Graham et al., 2016). One of the most common subtypes of cerebral palsy is unilateral spastic cerebral palsy (USCP) representing up to 34% of all cases (Pakula et al., 2009; Shevell et al., 2009; Wichers et al., 2005). In addition to motor symptoms, associated impairments can be present in children with USCP including deficits of cognition, language, memory, executive functions, sensory functions, sensory-motor integration and visuospatial attention.

Visuospatial attention is defined as the ability to orient to salient visual stimuli (Corbetta and Shulman, 2002; Petersen and Posner, 2012). Visuospatial neglect is a lateralized deficit of attention orientation leading to the neglect of stimuli which may occur in different frames of references: either an ego- or an allocentric frame of reference (Halligan et al., 2003; Walker, 1995). In egocentric neglect, patients neglect stimuli presented on one side of their body midline, while in allocentric neglect, patients neglect stimuli presented on one side of an object's midline. Visuospatial neglect has been for long highlighted in children with USCP in the egocentric frame of reference using mostly cancellation tasks (Lidzba et al., 2006; Trauner, 2003). Recently, visuospatial attention deficits were investigated using both ego- and allocentric tasks showing possible deficits in the allocentric frame of reference too and highlighting a differential deficit of ego and allocentric abilities depending on the brain lesion side (Ickx et al., submitted). Children with left USCP omitted more stimuli on the paretic side in the star cancelation task, an egocentric test, than children with right USCP. In turn, children with right USCP presented more often a deficit in the line bisection test, an allocentric test. In both frames of reference, visuospatial attention deficits could be influenced or mismatched by the presence of ophthalmological deficits. Atkinson et al. showed notably that infants with hyperopia (or farsightedness: refractive error which leads patients to have more difficulties to see close objects compared to farer ones) present lower performance in different visuomotor and visuocognitive tests (Atkinson et al., 2002). In another study, Cavézian et al. highlighted that children with ophthalmological deficits such as strabismus, amblyopia or refractive errors (hyperopia, myopia, astigmatism) are performing poorer in paper and pencil tests assessing visuospatial attention (e.g. teddy bear cancelation test, symbol cancelation task), shape matching tests, symbol orientation tasks and embedded figure tests. (Cavézian et al., 2012).

Ophthalmological impairments have been previously reported in a majority of children with cerebral palsy with a prevalence ranging from 40 to 90% of the children (Fazzi et al., 2012; Kozeis et al., 2007). In children with USCP, previous studies highlight the presence of refractive errors in almost 90% of the children. More than 60% of the children with USCP present lower or no stereopsis (Fazzi et al., 2012). Strabismus has also been reported in more than 50% of the children with USCP with similar occurrence of esotropia and exotropia. On the other hand, abnormal color perception or structural abnormalities are almost absent in most children with USCP (Fazzi et al., 2012; Kozeis et al., 2007). These previous studies highlighted that ophthalmological impairments are frequently observed in children with USCP, and are likely to have an effect on visuospatial attention. Disentangling the relationship between both is of importance since a good visual feedback is essential for manipulation in activities of the daily life and rehabilitation strategies to improve visual or visuospatial deficits are different.
Treatment of ophthalmological and visuospatial deficit differs largely. Indeed, ophthalmological deficits are usually treated with corrective glasses, eye patching, surgery, pharmacological methods, orthoptic

exercises or behavioral compensation (Aziz et al., 2006; Bagolini et al., 1986; Cho et al., 2009; Collins, 2014; Debert et al., 2016; Fortis et al., 2013); while the main methods of rehabilitation of visuospatial neglect consist in prismatic adaptation, limb activation therapy and visual scanning therapy (Luauté et al., 2006b; Priftis et al., 2013).
The aim of this study is to investigate the relationship between visuospatial deficits and ophthalmological impairments in children with USCP. We hypothesize that while both impairments are present in children with USCP, visuospatial attention deficits would not be directly related to ophthalmological impairments in children with USCP.

Methods

Participants:
Fifteen children with unilateral cerebral palsy (8 girls, mean age=10y11m (*SD*=2y11m)) were recruited among children who were previously enrolled in HABIT-ILE rehabilitation camps. Thus, inclusion and exclusion criteria were the same as in previous HABIT-ILE studies and included: (1) age between 6 and 13 years, (2) having an upper extremity motor impairment upon clinical examination, (3) being able, with the more affected upper extremity (UE), to grab light objects and to lift them 15 cm above a table, (4) educational level equivalent to the level of same aged typically developing children, (5) ability to follow up on instructions and to complete experimental assessments. Exclusion criteria were the presence of uncontrolled seizures. Potential participants were contacted by e-mail and by phone. The Ethics committee of Cliniques universitaires Saint-Luc, Université catholique de Louvain, Belgium, approved the study in accordance with the principles of the Declaration of Helsinki (reference number: B403201316810).

Assessments tools:

Ophthalmological assessments

Children received a thorough ophthalmological examination. This examination consists in assessments of the visual, binocular and refractive functions as well as of the ocular health. All ophthalmological assessments were carried out by an experienced ophthalmologist at the Clinique universitaire Saint-Luc, Université catholique de Louvain, Belgium.

Visual function assessment:

Visual acuity: Visual acuity in near and far space was evaluated using logMar chart, while children wore their usual correction. Visual acuity was scored from 0 to 10, 10 being the best visual acuity possible. The correspondence between the score on 10 and the minimum angle of resolution (MAR) was the following: 1/10= 10' (minutes of arc); 2/10=5'; 3/10=3.33'; 4/10= 2.5'; 5/10=2'; 6/10= 1.66'; 7/10=1.42'; 8/10= 1.25'; 9/10= 1.11'; 10/10= 1' (Elliott, 2008).

Visual field defect: visual field deficits were assessed using Goldmann visual field perimetry. In the Goldmann visual field perimetry, patients have to maintain fixation on a central point, the patient's fixation is controlled by a trained perimetrist, while a visual stimulus is moved around the patients' visual field. The patients have to report by pressing a button, if they can see the target or not. The visual field of the patient is then plotted. Results of the visual field perimetry are reported as being normal (no reduction of the visual field) or as presenting a reduction of the visual field as hemianopsie or quadranopsie. For a complete description of the Goldmann perimetry test, see Dersu et al. (2006).

Color Perception: the perception of color was assessed using the Hardy-Rand-Rittler (HRR) test. This test is composed of 6 plates allowing for the detection of deutan, protan and tritan deficiencies as well as 14 plates designed to grade the severity of the deficits. The absence or

presence of a color perception deficit is reported for each child (Birch, 1997).
Refractive error: refractive error was assessed under cycloplegia (cycloplegil 1%+tropicamide 1mg/ml) with an autorefractor. Refractive error is reported for both eyes in diopter, as well as the astigmatism error (in diopter) and its angle (in degree) (Elliott, 2008).

Binocular vision assessment:
Worth's test: This test assesses the binocular vision. It is composed of four dots placed in a cross-like fashion, 2 greens, 1 red and 1 white. The children wear red/green glasses, and are asked to report the number of dots they see. As the eye viewing through the red glass only sees the red and white dots, and the eye viewing through the green glass only sees the two green and the white dots, this assessment allows to test the fusion and/or the suppression of the eyes by asking the patients how many dots they can see and their location. The presence of eyes fusion or suppression was assessed and reported for each child (Roper-Hall, 2004).
TNO test: The TNO allows to assess the stereopsis and stereoacuity. It is composed of stereoscopics pictures/plates viewed through red/green glasses and it measures stereoacuity in seconds of arc (") from 480" to 15". The plates testing stereoacuity are composed of 2 discs with a missing parts (presented as a cake with a missing piece to the patient). The patients are asked to point to a missing part in each "cake". The performance of the children was registered as its stereoacuity in second of arc (") (Walraven and Janzen, 1993).
Cover test: This test assesses the patient's strabismus by alternatively suppressing binocular vision of one eye. Two versions of this test were used: in the far and in the near space. In both versions of the test, the children had to maintain fixation on a target (at 3 meters in the far version and 50cm in the near version) while the ophthalmologist alternatively covers and uncovers the patient's left or right eye. The ophthalmologist paid attention to a shiftlike movement of the eyes

which denotes the presence of strabismus. The power of strabismus was quantified by using prims diopters placed in front of the eyes when strabismus was detected. The power of strabismus reported is the power of the prism diopter needed to be placed in front of the eyes to suppress its deviation in the cover test (Elliott, 2008; Rainey et al., 1998).

Bi-Prisms test: This test is used to assess binocular vision and to have information about the fixating eye. In this test, two prisms of 6 diopters with opposite base, superposed, are placed alternatively in front of the patients' eyes while they maintain fixation on a target (located at 3m). The ophthalmologist records the movement of the eyes following the change of prism which provides information on the fixating eye.

Near point of convergence: This test assesses the position of the nearest point in which binocular vision can be maintained. It is assessed by asking the patients to maintain fixation on a target located at 50 cm and on the patients' midline. The target is then moved towards the patients. The near point of convergence is recorded as the point where the patients loses convergence. It is recorded in centimeter, 0 would be the best score possible and indicates a point of convergence on the tip of the nose (Elliott, 2008; Siderov et al., 2001).

Eyes motility assessment: The Broad H test was used to assess eyes motility. In this test, the children are asked to follow a target (a penlight) which is moved in an H pattern to the edge of the binocular field. The ophthalmologist has to record any misalignments of the patients' eyes which could indicate eyes motility deficits. Eyes Motility have been reported as normal or impaired (Elliott, 2008).

Ophthalmological health:

The anterior and posterior segment were examined using a slit lamp and the eyes fundi were examined under cycloplegia with an indirect binocular ophthalmoscopy. The presence of relative afferent pupillary defect as well as the presence of photomotor reflexes were assessed and reported if present.

Visuospatial assessments

Visuospatial assessment consists of 6 different tests assessing ego- and/or allocentric visuospatial attention. Reference values to the following tests are available for typically developing children of the same age range (Ickx et al., 2017). Visuospatial assessments were conducted in the same session as the ophthalmological assessments and before the cycloplegic drug was administered to children. Scores obtained by the children were compared with the relative values and reported in z-score or percentiles for the different tests.

Star cancellation: The test consists of an A4 sheet of paper with stars of two different sizes as well as distractor words which are semi-randomly distributed. The child is asked to cancel all small stars. The following variables are recorded: the number of stars omitted on each side (left, right) and the total number of omitted stars (Wilson et al., 1987). The absolute difference between the number of left omitted stars and right omitted stars is also computed. The variable recorded is the total number of omitted stars. Star cancellation mainly assesses egocentric neglect (Keller et al., 2005).

Ogden figure copy: This test consists of a drawing copy task. The child is asked to copy a figure (a house and 4 trees). The score ranges from 0 (no omissions) to 4 (multiple omissions) (Ogden, 1985).Ogden figure copy assesses both ego-and allocentric neglect (Medina et al., 2009).

Line bisection: The line bisection test consists of 2 pages with 10 lines of different lengths on each page. The child is asked to indicate the middle of each line by making a mark with a pencil. The deviation from the centre, in percentage of half the line length, is computed with the following formula:

Deviation= (b-a)/a*100

where a= half length of the line and b = distance between the beginning of the line and the mark made by the child (Scarisbrick et al., 1987). The variable used to determine if a child with USCP presents with an abnormal value compared to reference values is the average deviation (in percentage) from the centre of each line. Line bisection test assesses allocentric neglect. An error towards the paretic side of space is recorded as a negative value.

Proprioceptive pointing: The child is blindfolded and seated in front of a table. A paper sheet with angled graduation lines (deviation in degrees) from a central point is aligned with the body midline of the child. The child is asked to point straight ahead on the table with the index finger of his/her less affected upper limb (Riquelme et al., 2015). The pointing is performed three times. The variable recorded is the average deviation (mean of the three pointings in degrees) with regards to the child's body midline. Proprioceptive pointing assesses egocentric neglect. A deviation towards the paretic side of space is recorded as a negative value.

Visuo-proprioceptive pointing: The child is seated in front of a table with his body midline aligned with the midline of a half-open wooden box (with a transparent side) on the table. The box is large enough to place the child's less affected arm inside without having visual feedback of the arm. The child is asked to point with his index finger towards three different targets 0°, -21° and + 21° of the body midline (Frassinetti et al., 2002; Riquelme et al., 2015). Each target is presented three times in a random order. The variable recorded is the average deviation from the target (mean of the 9 pointings in degrees). Visuo-proprioceptive pointing assesses allocentric neglect. A deviation towards the paretic side of space is recorded as a negative value.

Statistical analysis:

Descriptive statistics:

Descriptive statistics were computed for the different variables. For ophthalmological assessments, results of each child are presented in

Table 1. For visuospatial assessments, quartile for the star cancellation test and Ogden figure copy test or z-score for the line bisection test, proprioceptive pointing and visuo-proprioceptive pointing are presented in Table 2.

Correlation:

Spearman rho's were computed between the different visuospatial assessments and the Worth's test, the TNO test, the Covertest, the visual field test and both eyes' visual acuity. To run these analyses, the variables of the different tests (the six visuospatial assessments as well as the worth test, the TNO, covertest and the assessment of the visual field) were categorized. For the visuospatial tests, results were coded according to normative values quartile (star cancellation and Ogden figure copy: 5 categories, one for each quartile, plus one for score outside the 95th percentile) or to the absolute values of z-scores (line bisection, proprioceptive pointing and visuo-proprioceptive pointing) as presented in table 2. For the worth test, two categories were created; eyes fusion or eyes suppression. For the TNO test, three categories were created: normal stereoscopic vision (stereoacuity ≤60"), subnormal stereoscopic vision (stereoacuity>60") and no stereoscopic vision. For the covertest, three categories were created; no strabismus, presence of esotropia and presence of exotropia. For the assessment of the visual field, three categories were created; no visual field impairment, presence of hemianopsia and presence of quadrianopsia. For eyes acuity, the values of acuity reported in table 1 were used (score for each eyes on 10).

Fisher's exact test:

Due to the small sample, Fisher's exact test was used to investigate association between ophthalmological and visuospatial impairments. Contingency tables were created using variables categorize in two or three categories. For the visuospatial assessment, a child was considered as "impaired" when outside of the normative values for his age as described in Ickx et al. (2017). For the worth test, two categories were created; a child was considered as “impaired” if suppression of one eye was present. For the TNO test, three categories were created: normal stereoscopic vision (stereoacuity ≤60”), subnormal stereoscopic vision (stereoacuity>60”) and no stereoscopic vision. For the covertest, two categories were created; a child was considered as “impaired” if he presented any kind of strabismus. For the assessment of the visual field, two categories were created; a child was considered as “impaired” if he presented a reduction of his visual field.One fisher’s exact test was computed for each pair of ophthalmological/visuospatial tests.

Results

Descriptive statistics:

Ophthalmological assessment:

Individual results are presented in Table 1. The sample included 8 girls and 7 boys, with a mean age of 10y11m (*SD*=2y11m), 8 presented right USCP and 7 left USCP. One child presented a visual acuity of less than 7/10. 28.6% of the children tested (4 children) presented a visual field reduction. No children had color perception deficits. One child presented the suppression of one eye on the worth 4 dots test. 46.7% of the children (7) had a binocular acuity less than 60” as measured by the TNO test. 40% of the children (6) presented strabismus as measured by the cover test, no difference for the strabismus power were observed between the near and far distance in the sample. The bi-prism test showed that 26.7% of the children (3) did not have a preferred eye of fixation, while 26.7% (3) preferred their right eye and 46.7% (7) preferred their left eye. 1 child had a near point of convergence farther than the tip of the nose. Slit lamp examination did not highlight any deficits in the present sample. The examination of eye fundi showed the presence of malformation in three children, 2 had malformation present in only one eye while the third presented it in his both eyes. Relative afferent pupillary defect was found in two children.

Subject	Age	Sex	Most affected side	Visual accuity		Worth's test	bi-prism test	TNO	Cover test (power)		Visual field	photomotor reflexe
				Left eye	Right Eye				Close	Far		
1	5	F	Left	8	10	Fusion	Right eye dominant	500"	Eso (0)	Eso (0)	ok	ok
2	6	M	Left	10	10	Fusion	Right eye dominant	60"	Ortho (0)	Ortho (0)	NA	ok
3	8	M	Left	9	9	Fusion	No dominance	60"	Ortho (0)	Ortho (0)	ok	ok
4	8	F	Left	10	10	Fusion	No dominance	60"	Ortho (0)	Ortho (0)	ok	ok
5	9	M	Left	10	10	Fusion	Left eye dominant	240"	Exo & R Hyper (12)	Exo & R Hyper (14)	quadranopsia	ok
6	10	F	Left	9	9	Fusion	Left eye dominant	60"	Ortho (0)	Ortho (0)	ok	ok
7	10	M	Left	8	8	Fusion	No dominance	60"	Ortho (0)	Ortho (0)	ok	ok
8	10	M	Left	9	8	Fusion	Left eye dominant	240"	Exo (16)	Exo (18)	ok	ok
9	11	F	Left	4	3	Supression	Left eye dominant	500"	Exo (0)	Exo (14)	hemianopsia	ok
10	11	F	Left	9	7	Fusion	Left eye dominant	240"	Ortho (0)	Ortho (0)	ok	ok
11	11	M	Left	8	8	Fusion	Left eye dominant	500"	Ortho (0)	Ortho (0)	hemianopsia	ok
12	13	F	Left	9	10	Fusion	Right eye dominant	60"	Exo (8)	Exo (20)	ok	ok
13	13	F	Left	10	10	Fusion	Right eye dominant	60"	Ortho (0)	Ortho (0)	ok	ok
14	13	F	Left	10	10	Fusion	No dominance	60"	Ortho (0)	Ortho (0)	ok	ok
15	17	M	Left	10	10	Fusion	Left eye dominant	500"	Eso (8)	Eso (4)	hemianopsia	ok

Cover test : Ortho= Orthotropia ; Eso= Esotropia ; Exo= Exotropia; Hyper= Hypertropia

Table 1 A: Ophthalmological data of each child.

Subject	Age	Sex	Most affected side	afferent pupillary deficit	Near point of convergence	Slit lamp examination	Eye fundi examination	Eye refraction				Eye motility
								Left eye refraction	Left eye astigmatism (angle)	Right eye refraction	Right eye astigmatism (angle)	
1	5	F	Left	Absent	0 cm	Ok	0	3,75	-0,5 (20°)	4	-0,5 (145°)	Ok
2	6	M	Left	Absent	0 cm	Ok	0	1,25	-0,5 (180°)	1	-0,25 (160°)	Ok
3	8	M	Left	Absent	0 cm	Ok	0	1	-0,25 (160°)	1	-0,25 (60°)	Ok
4	8	F	Left	Absent	0 cm	Ok	0	1,5	0 (0°)	1,25	0 (0°)	Ok
5	9	M	Left	Absent	0 cm	Ok	1	2,25	-0,75 (180°)	2,5	-2 (10°)	Ok
6	10	F	Left	Absent	0 cm	Ok	0	1,25	-0,25 (175°)	1,5	-0,25 (10°)	Ok
7	10	M	Left	Absent	0 cm	Ok	0	1,25	-0,25 (15°)	1,5	-0,25 (80°)	Ok
8	10	M	Left	Absent	0 cm	Ok	0	-0,25	-0,25 (155°)	-1	-0,25 (170°)	Left Eye deficit
9	11	F	Left	Absent	0 cm	Ok	2	2	-0,5 (140°)	2,5	-0,75 (170°)	Gaze evoked nystag
10	11	F	Left	Absent	0 cm	Ok	0	-0,25	-3,5 (175°)	-1	-3,5 (10°)	Ok
11	11	M	Left	Present	0 cm	Ok	0	-2,5	-0,75 (180°)	-2	-0,5 (30°)	Ok
12	13	F	Left	Absent	0 cm	Ok	0	-2,25	-1,5 (175°)	-1,75	-1,25 (35°)	Ok
13	13	F	Left	Absent	5 cm	Ok	3	0,5	-1 (30°)	0,5	-0,5 (155°)	Ok
14	13	F	Left	Absent	0 cm	Ok	0	1,5	-1 (5°)	2	-1,25 (170°)	Ok
15	17	M	Left	Present	0 cm	Ok	0	-1,5	-0,5 (165°)	-0,75	-0,75 (10°)	Gaze evoked nystag

Eye fundi examination: 1= Optic nerve ok, congestive vein; 2=Optic nerve dysplasia ; 3= left eye optic nerve hypoplasia

Table 1 B: Ophthalmological data of each child.

Subject	Age	Sex	Paretic Side	Total omitted stars (perc)	Ogden figure copy (perc)	Line bisection (z-score)	Proprioceptive pointing (z-score)	Visuo-proprioceptive pointing (z-score)
01	5	F	L	<95	<25	-2,31	1,59	-0,23
02	6	M	L	>95	>75	-3,00	0,35	-0,99
03	8	M	L	<50	<50	-0,04	-0,24	1,58
04	8	F	R	<95	>95	1,13	0,56	0,43
05	9	M	L	<25	>95	-2,95	-2,31	-1,60
06	10	F	R	<25	<95	0,50	-0,04	-1,23
07	10	M	R	<95	<95	1,41	-1,25	3,23
08	10	M	R	<50	>95	-1,19	1,08	0,17
09	11	F	R	>95	>95	2,37	2,03	-2,35
10	11	F	L	>95	>95	-1,31	0,81	-2,35
11	11	M	R	>95	<95	-0,36	0,35	0,45
12	13	F	R	<95	<75	-1,90	0,33	-0,87
13	13	F	R	<50	<75	-1,11	0,52	-0,99
14	13	F	L	<95	<75	1,02	1,32	-0,02
15	17	M	L	<95	<95	0,80	1,70	1,60

Table 2 : Visuospatial data of each child. Perc= percentile

Visuospatial assessment:

66.7% of the children assessed presented at least a deficit in a visuospatial attention test, 26.7% presented a deficit in the star cancellation test, 33.3% in the Ogden figure copy test, 40% in the line bisection test, 13.3% in the proprioceptive pointing and 20% in the visuo-proprioceptive pointing. Individual scores are presented in Table 2: in quartile (<25= first quartile; <50= second quartile; <75= third quartile; <95= fourth quartile; >95= score outside the normative values) for the star cancelation and the Ogden figure copy and in z-scores for the line bisection, proprioceptive pointing and visuo-proprioceptive pointing test.

Correlations:

Significant correlations were highlighted between the absolute values of the z-scores for the proprioceptive pointing and the results to the TNO test (r_s=-.58; p=0.023), the cover test (r_s=-.588; p=0.021) and the presence of a visual field defect (r_s=-.541; p=0.046).Significant correlations were highlighted between the presence of a visual field defect and the quality of stereoscopic vision deficit (r_s=.665; p=0.01), between the quality of stereoscopic vision deficit and the presence of strabismus (r_s=.645; p=0.009) and between the visual acuity of the left and of the right eyes (r_s=.723; p=0.002). Complete results are presented in Table 3.

Spearman correlation	Star cancellation deficit	Ogden figure copy deficit	Line bisection deficit	Proprioceptive pointing deficit	Visuo-proprioceptive pointing deficit	Binocular fusion deficit (Worth test)	Stereoscopic vision deficit (TNO test)	Presence of strabismus (cover test)	Visual field defect	Visual acuity LE	Visual acuity RE
Star cancellation deficit											
Ogden figure copy deficit	0.146 (0.603)										
Line bisection deficit	0.256 (0.356)	0.286 (0.301)									
Proprioceptive pointing deficit	0.099 (0.725)	0.331 (0.228)	0.452 (0.091)								
Visuo-proprioceptive pointing deficit	0.099 (0.727)	0.312 (0.258)	0.177 (0.527)	0.18 (0.521)							
Binocular fusion deficit (Worth test)	-0.357 (0.192)	-0.322 (0.242)	-0.309 (0.262)	-0.371 (0.173)	-0.341 (0.213)						
Stereoscopic vision deficit (TNO test)	-0.332 (0.227)	-0.264 (0.341)	-0.116 (0.681)	-.580* (0.023)	-0.101 (0.721)	0.375 (0.169)					
Presence of strabismus (cover test)	0.084 (0.765)	-0.021 (0.94)	-0.371 (0.173)	-.588* (0.021)	0.032 (0.911)	0.247 (0.374)	.645** (0.009)				
Visual field defect	-0.158 (0.591)	-0.389 (0.169)	-0.18 (0.538)	-.541* (0.046)	-0.34 (0.234)	0.391 (0.167)	.665** (0.01)	0.402 (0.154)			
Visual acuity LE	-0.296 (0.284)	-0.436 (0.104)	0.109 (0.699)	0.022 (0.937)	-0.43 (0.11)	0.472 (0.076)	0.308 (0.265)	-0.18 (0.52)	0.074 (0.8)		
Visual acuity RE	-0.31 (0.261)	0.035 (0.9)	-0.051 (0.857)	0.003 (0.992)	-0.214 (0.444)	0.458 (0.086)	0.411 (0.129)	0.147 (0.602)	0.023 (0.937)	.723** (0.002)	

*: p<.05

Table 3: Details of the different correlations

Fisher's exact test:
No relationship between the presence of an ophthalmological deficit and the presence of visuospatial deficits was found.

Worth's test: Children with a deficit in the Worth's test do not present more or less frequently a deficit in the star cancellation test (p=0.266), in the Ogden figure copy test (p=0.333), in the line bisection test (p=1), in the proprioceptive pointing test (p=1) or in the visuo-proprioceptive pointing test (p=1).

TNO test: Children with a deficit in the TNO test do not present more or less frequently a deficit in the star cancellation test (p= 0.3436), in the Ogden figure copy test (p= 0.343), in the line bisection test (p=0.496), in the proprioceptive pointing test (p=0.428) or in the visuo-proprioceptive pointing test (p=0.428).

Cover test: Children with a deficit in the cover test do not present more or less frequently a deficit in the star cancellation test (p=0.604), in the Ogden figure copy test (p=0.328), in the line bisection test (p= 0.135), in the proprioceptive pointing test (p=1) or in the visuo-proprioceptive pointing test (p=0.485).

Visual field: Children with a visual field defect do not present more or less frequently a deficit in the star cancellation test (p=0.175), in the Ogden figure copy test (p=0.580), in the line bisection test (p=0.580), in the proprioceptive pointing test (p=0.505) or in the visuo-proprioceptive pointing test (p=1).

Discussion

This study aimed to investigate a potential relationship between ophthalmological and visuospatial attention deficits in children with USCP. Ophthalmological impairments have been reported in almost half

the sample, with more than 45% of the children presenting a binocular acuity of less than 60” of arc and 40% of them presenting strabismus. Concerning the presence of visuospatial deficits, the results highlight a prevalence of deficits similar to those reported in a previous study (Ickx et al., 2017).
Correlations were solely observed between one test of visuospatial attention, the proprioceptive pointing test, and 3 ophthalmological measures: TNO test measuring stereopsis, cover test measuring strabismus and the presence of a visual field defect. The TNO test and the cover test allow together assessing the quality of binocular vision, i.e. the perception of depth arising from binocular horizontal retinal disparity (Fricke and Siderov, 1997).

This correlation is unexpected since children with USCP present less often a deficit in the proprioceptive pointing test (11.6% of the children presenting a deficit) than in other visuospatial attention tests (Ickx et al., submitted). This pointing test is actually related only to proprioception (no visual feedback). This correlation may suggest a proprioceptive compensation of the ophthalmologic deficit. It may also be that children with larger ophthalmological deficits also present other sensory deficits (tactile & proprioceptive) potentially explaining this relationship. Interestingly, Ego et al. (2014) reported that the development of eyes movements during the pursuit of a target in children with CP is close to that observed in typically developing children. However, the authors reported that children with CP present a pursuit deficit for target moving towards the side of their lesion. This may match our hypothesis of children with CP presenting a distorted internal representation of space.

Our results highlighted that children with USCP can either present no visuospatial attention deficits and no ophthalmological impairments, both deficits or only one of these deficits. This suggests a dissociation between the two kinds of deficits.

Such dissociation has already been highlighted in adult patients with brain lesions, especially regarding the different compensatory mechanisms following the initial lesion. Barton et al. (1998) showed that in a line bisection task, patients with left hemianopia directed more often their sight on the left side of the line, whereas patients with left neglect directed their sight almost only on the right side of the line. The same opposite patterns between patients with hemianopia and patients with neglect was observed in the line bisection results of several studies (Barton et al., 1998; Kerkhoff and Bucher, 2008; Mitra et al., 2010; Schenkenberg et al., 1980; Veronelli et al., 2014). Indeed, while patients with visual neglect deviate toward the ipsilesional side of the lines in line bisection tasks, hemianoptic patients present a deviation towards the contralesional side of the line, comparable, but bigger, to the systematic deviation to the left made by healthy subject (Barton et al., 1998; Kerkhoff and Bucher, 2008).
In our sample, 3 children presented hemianopia and one of them was outside the normative values in the line bisection test. However, the 2 others while still within the normative range showed a deviation towards the ipsilesional side in the line bisection test, which is opposite to previous observation made in chronic hemianoptic patients. Such results suggest potential differences between children with USCP and adult patients with an acquired brain lesion. Future studies should investigate the difference between these children in term of lesions location, characteristic and brain reorganization.

To conclude, visuospatial deficits and ophthalmological deficits are present in children with USCP. However, few relationships between these deficits have been highlighted. The major limitation of this study is the reduced sample size. Studies with a larger sample size are required in the future to investigate deeply this question. First results from this limited analysis suggest an absence of relationship between ophthalmological and visuo-spatial deficits. If confirmed this observation has large implications notably in terms of rehabilitation, since rehabilitation strategies for ophthalmological and visuospatial attention deficits differs largely while reduction of both deficits may be beneficial to improve visual feedback needed for daily life activities.

Chapter V: Randomized controlled trial of prismatic adaptation for visuospatial attention disorders in children with unilateral spastic cerebral palsy

Background: Though visuospatial attention deficits are reported in children with unilateral spastic cerebral palsy (USCP), no effective rehabilitation treatment has been described until now. In adults, prismatic adaptation (PA) - a rehabilitation technique with prismatic goggles shifting the visual field - is effective to treat visuospatial attention deficits (Rossetti et al., 1998). This study aimed at investigating the effectiveness of PA in children with USCP during a bimanual intensive therapy.

Method: 30 children with USCP (left-sided n = 11, aged 6 to 16 yrs) were included. During a Hand Arm Bilateral Intensive Therapy Including Lower Extremities (HABIT-ILE, 90 hours over 10 days), children received a bimanual task intervention of 20 minutes twice daily wearing either sham or prismatic goggles (11° shift of the visual field towards the paretic side). Effect of time (pre-intervention/post-intervention) and effect of group were investigated using two ways repeated measures ANOVA or Wilcoxon rank test on associated samples (time) or Kruskal-Wallis (group).

Results: Star cancellation improved significantly after HABIT-ILE, regardless of the type of visuospatial intervention (TIME: p=0.026). More specifically, there was a significant effect of TIME in children with left hemiparesis for the line bisection test and a tendency for an effect of TIME for the left omitted stars. In children with right USCP a significant effect of TIME was observed for the right omitted stars No significant effects of GROUP were observed.

Conclusion: An intensive bimanual motor therapy as HABIT-ILE is effective to improve visuospatial attention skills, particularly in children with left hemiparesis.

No significant effect of concomitant prismatic adaptation could be observed on visuospatial deficits in USCP children.

Introduction

Cerebral Palsy (CP) occurs in 2 to 3.6 out of a thousand live births and results from brain lesions during prenatal, perinatal or early postnatal life. Unilateral spastic cerebral palsy (USCP) is one of the most common subtypes of CP which represents up to 34% of all cases (Pakula et al., 2009; Shevell et al., 2009; Wichers et al., 2005; Yeargin-Allsopp et al., 2008). The main feature of CP is the motor impairment which depends on the timing, localization and size of the brain lesion as well as on the child's cortical reorganization and recovery. Additional impairments include deficits of cognition, language, sensory functions and sensory-motor integration (Bleyenheuft and Gordon, 2013; Straub and Obrzut, 2009). Visuospatial attention deficits have been reported in children with USCP (Laurent-Vannier et al., 2003; Trauner, 2003). Both egocentric visuospatial attention (i.e. the patient neglects stimuli presented on one side of the hemispace referred to his body's midline) and allocentric visuospatial attention (i.e. the patient neglects stimuli on one side of the object's midline) may be affected, with different deficit patterns between children with predominating left or right brain lesions (Ickx et al. submitted). Most rehabilitation interventions in children with CP aim at improving motor function and their everyday life independence (Novak et al., 2013). Few rehabilitation interventions have been designed to improve associated impairments of children with CP and more specifically, to our knowledge no rehabilitation treatment has been investigated for its effectiveness on visuospatial deficits. This is striking as visuospatial attention deficits have a prevalence of more than 50% in children with CP (Ickx et al.) and are known to impair motor control and independence in everyday life activities in adult stroke survivors (Harvey and Rossit, 2012; Meyer et al., 2016). Prismatic adaptation and vestibular stimulation are used for visuospatial attention rehabilitation in adult patients (Fasotti and van Kessel, 2013; Luauté et al., 2006b). Prismatic adaptation uses prismatic goggles to induce a lateral shift of the visual field (generally directed towards the neglected side) which leads to a recalibration of visuomotor coordinates coined the ‘after-effect’ (Rossetti et al., 1998). In order to be effective, prismatic goggles should be worn while executing visuomotor tasks such as pointing tasks, ecological tasks or therapeutic games (Frassinetti et al., 2002; Riquelme et al., 2015; Rossetti et al., 1998). Daily prismatic adaptation sessions are proposed for rehabilitating adult patients with visuospatial neglect. Prismatic rehabilitation induces short-term and long-term effects on visuospatial attention as well as on daily life activities (Frassinetti et al., 2002; Luauté et al., 2006c; Newport and Schenk, 2012). A single session of prismatic adaptation can induce a visuomotor after-effect in children with USCP (Riquelme et al., 2015). The effectiveness of repeated sessions of prismatic adaptation as a rehabilitation treatment for visuospatial attention deficits in children with CP has not been investigated so far.

The aim of this randomized controlled trial was to investigate the effectiveness of prismatic rehabilitation in children with USCP during a bimanual intensive therapy. Outcomes were: (a) motor function as measured by the Jebsen Taylor Test of Hand Function (JTTHF) and (b) measurements of ego- and allocentric visuospatial attention. Prismatic rehabilitation intervention and sham intervention were administered during an intensive rehabilitation camp for children with USCP based on the Hand Arm Intensive Bimanual Therapy Including Lower Extremities (HABIT-ILE) rehabilitation method. HABIT-ILE is a motor-skills learning based therapy that combines intensive bimanual, posture and lower extremities therapy (Bleyenheuft & Gordon, 2014).

Methods

Participants:

Participants were recruited in collaboration with centers dedicated to the treatment of children with Cerebral Palsy in Belgian university hospitals. Potential participants were contacted by e-mail or phone.

Children who were interested and available to participate were evaluated during a baseline clinical examination. Children were classified according to the Manual Ability Classification System (Eliasson et al., 2006). In addition, when MRI was available brain lesions were classified by a neuroradiologist using the criteria of Krägeloh-Mann and Horber (Krägeloh-Mann and Horber, 2007), allowing to define the origin/timing of their brain lesion. The inclusion criteria were: (1) age between 6 and 13 years, (2) upper extremity motor impairment upon clinical examination, (3) ability to grab light objects with the more affected upper extremity (UE) and lift them 15 cm above a table, (4) educational level equivalent to the level of same aged typically developing children, (5) ability to follow up on instructions and complete experimental assessments. Exclusion criteria were: (1) presence of uncontrolled seizures, (2) orthopedic surgery and/or botulinium toxin injection within the previous 6 months or planned during the study. The Ethics committee of Cliniques universitaires Saint-Luc, Université catholique de Louvain, Belgium, approved the study in accordance with the principles of the Declaration of Helsinki (reference number: B403201316810).

Design:

This study ran during three consecutive HABIT-ILE summer camps held in Brussels, Belgium. Children were randomized off-site to one of two intervention groups, balanced and stratified by age and lesion side, on the first day of the summer camp: (1) prismatic intervention + HABIT-ILE or (2) sham intervention + HABIT-ILE. The total duration of the intervention (prismatic or sham) was 320 minutes (two daily sessions of 20 minutes during 8 days). Children were aware that different types of goggles were used for the intervention. However, they were not informed of the existence of sham goggles and were unable to compare each other's goggles as the intervention sessions took place on a one-to-one basis with a dedicated interventionist in a separate room. Interventionists who provided the prismatic (or sham) intervention were different from the interventionists who provided HABIT-ILE therapy.

Prismatic intervention:

Children randomized to the prism intervention group wore prismatic glasses inducing a visual field lateral shift of 20 prism diopters (~11°). The deviation induced by the prismatic glasses was chosen towards the less affected side of each child with the objective to induce a visuo-motor after-effect towards the more affected side.

Sham intervention:

Children randomized to the sham intervention group wore sham glasses that did not alter the visual field.

Visuomotor task:

While wearing prismatic or sham goggles, participants performed common children games selected for promoting horizontal exploration of space and visuo-motor interaction in both sides of hemispace, as described by Riquelme et al. (2015). Vision of both UE was available for the whole movement path. A variety of games was proposed to obtain sustained collaboration and attention of children during 20 min. Different game activities were individually selected in accordance with each child's manipulative and reading skills.

There were different categories of games: puzzles (2-D and 3-D puzzles), construction games (click assemblage, fitting small geometrical pieces in corresponding holes as fast as possible), board games (copying a chessboard pattern, copying or composing words with square-cardboard letters, family board game) and memory games (matching cards or discovering hidden objects). Each game came in various forms and difficulty levels (example: 2D-puzzle with 4 pieces, 2D-puzzle with 20 pieces, 3D-puzzle).

HABIT-ILE rehabilitation:

Summer camps were held in Brussels during the summers of 2013, 2014 and 2015. The camps lasted for 2 consecutive weeks (5 days/week) during which children received 90 hours of HABIT-ILE (9 hours/day) by trained interventionists. Interventionists were either physiotherapy (PT)/occupational therapy (OT) students (n=22), certified PT (n=7) or certified OT (n=3). Interventionists were asked to provide HABIT-ILE procedure exclusively, for which they were trained before the camp on the basis of a procedures manual. A minimal ratio of 1 interventionist for 1 child was maintained during all camps. Interventionists were paired with children using a family-centered approach, considering parents' and supervisors' recommendations (for a detailed description of HABIT-ILE: see Bleyenheuft et al., 2014) . In brief, HABIT-ILE is an intensive, bimanual, motor-learning based therapy similar to HABIT, incorporating a lower extremities and postural component. HABIT-ILE uses structured bimanual tasks in combination with constant trunk and lower extremity stimulation. The difficulty of tasks increased during the camp, as children improved their skills, in order to induce increasing bimanual coordination, and upper and lower extremities postural control. Tasks were selected depending on the child's initial impairments and in accordance with functional goals determined by children and their parents before the camp. The efficiency of HABIT-ILE for improving both UE function and walking abilities has been previously demonstrated in children with USCP (Bleyenheuft et al., 2015).

Outcome measures:

Motor assessment:

Jebsen Taylor Test of Hand Function (JTTHF):

The JTTHF assesses the upper extremity function using several timed subtests mimicking everyday life unimanual actions (flipping cards, moving objects, simulated eating, stacking checkers, manipulating light objects and manipulating heavy objects). The score is the addition of the time taken to finish the different subtests. If the child has not reached the goal of the subtest after 180 seconds, the child has a score of 180 for this subtest and is asked to perform the following subtest. Therefore, the maximum score is 1080 (6*180s).

Visuospatial assessments:

Star cancellation: The test consists of an A4 sheet of paper with stars of two different sizes as well as distractor words which are semi-randomly distributed. The child is asked to cancel all small stars. The following variables are recorded: the number of stars omitted on each side (left, right) and the total number of omitted stars (Wilson et al., 1987).

Ogden figure copy: This test consists of a drawing copy task. The child is asked to copy a figure (a house and 4 trees). The score ranges from 0 (no omissions) to 4 (multiple omissions) (Ogden, 1985).

Reading: This test consists of reading out loud a text. Only children over 7 years old with sufficient reading skills performed this test. The following variables are recorded: the total number of omitted words, the total number of substitutions, and the time needed to perform the test (Reinhart et al., 2013).

Line bisection: The line bisection test consists of 2 pages with 10 lines of different lengths on each page. The child is asked to indicate the middle of each line by making a mark with a pencil. The deviation from the centre, in percentage of half the line length, is computed with the following formula:

deviation= (b-a)/a*100

where a= half length of the line and b = distance between the beginning of the line and the mark made by the child (Scarisbrick et al., 1987).

Proprioceptive pointing: The child is blindfolded and seated in front of a table. A paper sheet with angled graduation lines (deviation in degrees) from a central point is aligned with the body midline of the child. The child is asked to point straight ahead on the table by moving the index finger of the less affected UE (Riquelme et al., 2015). The pointing is performed three times. The variable recorded is the average deviation (mean of the four pointings in degrees) with regards to the child's body midline (Riquelme et al., 2015).

Visuo-proprioceptive pointing: The child is seated in front of a table with his body midline aligned with the midline of a half-open wooden box (with a transparent side) on the table. The box is large enough to place the child's less affected UE inside without having visual feedback of the UE. The child is asked to point with his index finger towards three different targets 0°, -21° and + 21° of the body midline (Frassinetti et al., 2002; Riquelme et al., 2015). Each target is presented three times in a random order. The variable recorded is the average deviation from the target (mean of the 9 pointings in degrees).

Standardization of the data:

Variables of line bisection, proprioceptive pointing and visuo-proprioceptive pointing were standardized in such a way that negative values indicated a deviation towards the more affected side. In right paretic children, the values "a" became "-a" after the standardization.

Statistical analysis:

Normality of distribution and homogeneity of variance were assessed for the different variables using Kolmogornov-Smirnov test and Levene's tests. Effect of handedness on the baseline visuospatial assessments was investigated using one way analysis of variance (ANOVA) for parametric variables or Kruskal-Wallis for non-parametric variables. Interactions were investigated using two ways ANOVA with TIME as within-subjects factor (two levels: Pre intervention vs. Post intervention) and GROUP as between-subjects factor (two levels: Prism vs. Sham) for parametric variables. For non-parametric variables, the effect of TIME was investigated using Wilcoxon rang test on associated samples and the effect of GROUP was investigated using a Kruskal-Wallis test on the difference between Post-intervention and Pre-intervention scores with the factor GROUP as between-subjects factor. Analyses were run on the entire study population as well as separately on children with Left and Right USCP as described in a previous study (Ickx et al 2018).

Spearman correlations were computed to assess the relationship between motor function and visuospatial attention variables before the intervention as well as changes due to the intervention.

For all statistical analyses, SPSS 22 software was used and the significance level was set at $p<0.05$.

Results

Participants:

30 children with USCP took part in this study (mean age: 8.9 yrs. (±2.64)) 11 with left USCP, 19 with right USCP. Fifteen children were included in the prism intervention group (6 with left USCP and 9 with right USCP) and 15 children were included in the sham intervention group (5 with left USCP and 10 with right USCP). Children were classified according to the Manual Ability Classification System as levels I (n=5) or II (n=25). Using the criteria of Krägeloh-Mann and Horber brain lesions were classified as: cortical malformation (n=3), periventricular lesion (n=10) and cortical/subcortical lesion (n=16) (MRI missing, n=1). Details of the demographic and clinical data are summarized in Table 1.

Table1: Demographic and clinical characteristics of children

General Characteristics		More affected upper extremity		
		Sham	Prism	All
Age (*SD*)		8y10m (2y8m)	9y1m (2y7m)	8y11m (2y7m)
Gender (N)	Female	7	8	15
	Male	8	7	15
More affected UE	Left	10	9	19
	Right	5	6	11
Lesion Timing (N)	Brain malformation	1	2	3
	Periventricular white matter lesion	4	6	10
	Cortical/subcortical lesion	9	7	16
	NA	1	0	1
MACS (level)	Level I	4	1	5
	Level II	11	14	25
Total (N)		15	15	30

MACS= Manual Ability Classification System

Handedness:

An effect of handedness (affected side) was found for the line bisection test (*F(1; 29)*=25.706; *p*<0.0001). Children with right USCP (left brain lesion) presented a mean deviation of 7.07% (SD=8.131), indicating a deviation towards the less affected side while children with left USCP presented a mean deviation of -6.74% (SD=5.091) indicating a deviation towards the more affected side. Due to the effect of handedness on the line bisection test and as previous authors have shown differences between children with left and right USCP (Ickx et al., submitted), results of the different visuospatial attention assessments were analyzed in children with a left or right USCP independently.

Motor assessment:

JTTHF scores of the less affected and of the more affected UE are described in Figures 1 A and B. In the entire study population, two-way ANOVA showed a significant TIME effect: $F(1;28)=5.992$; $p=0.021$. No significant effects were observed for the factor GROUP or the interaction TIME*GROUP (all $p>0.339$). In children with right USCP, a significant effect was found for the factor TIME: $F(1;17)=8.433$; $p=0.01$) and no significant effects were found for the factor GROUP or interaction TIME*GROUP (all $p>0.751$). In children with left USCP, no significant effects were observed (all $p>0.196$).

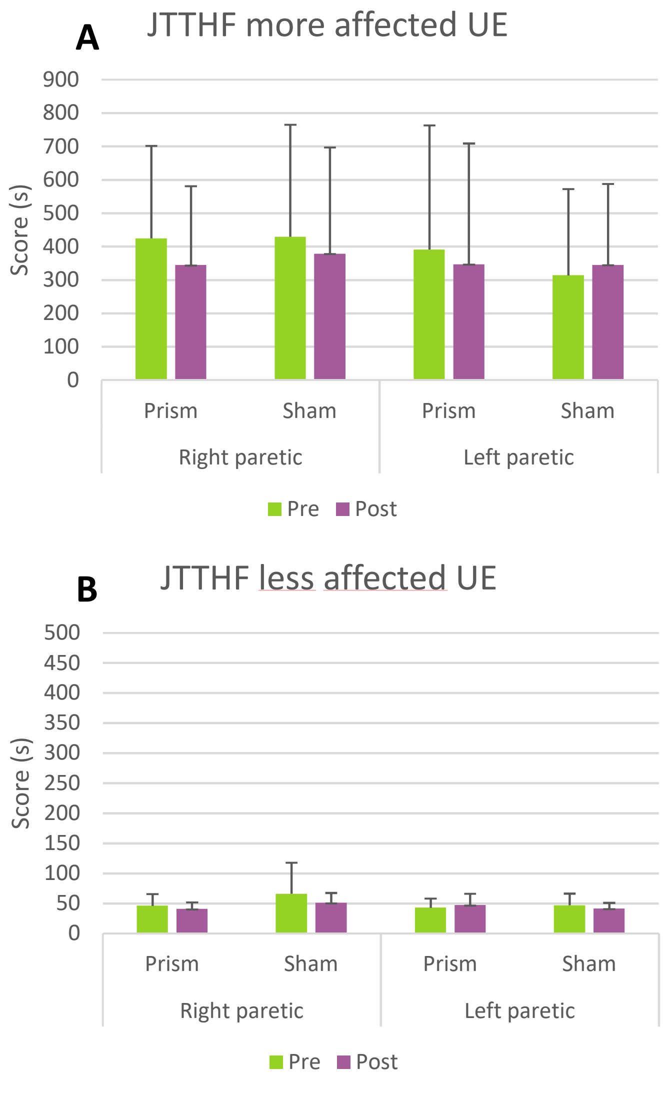

Figure 1: Score (s) of respectively (A) the more affected UE and (B) the less affected UE in the Jebsen Taylor Test of Hand Function for children with right or left USCP in the prism or sham group before and after the therapy. Bars represent the mean, and error bars represent one standard deviation.

Visuospatial assessments:
The scores of the different visuospatial assessments for the different groups (sham/prism; left paretic/right paretic) are described in Figures 2 and 3.

Ogden figure copy: No significant effects were observed in the entire study population (all $p>0.248$), neither in children with right USCP (all $p>0.705$) nor in children with left USCP (all $p>0.180$) (Figure 2A).

Star cancellation test: All omitted stars: in the entire study population, the Wilcoxon rank test indicated a significant effect of the factor TIME ($Z=-2.28$; $p=0.023$), while no significant effects were observed for the factor GROUP ($p>0.264$). No significant effects were observed in children with right USCP (all $p>0.106$) nor in children with left USCP (all $p>0.071$) (Figure 2B).
Left omitted stars: No significant effects were observed in the entire study population (all $p>0.137$), neither in children with right USCP (all $p>0.403$) nor in children with left USCP (all $p>0.068$) (Figure 2C).
Right omitted stars: For the entire study population, Wilcoxon rank test indicated a significant effect of the factor TIME ($Z=2.220$; $p=0.026$); no significant effect was observed for the factor GROUP ($p>0.153$). In children with right USCP, Wilcoxon rank test indicated a significant effect of the factor TIME ($Z=-2.231$; $p=0.026$), while no significant effect was observed for the factor GROUP ($p>0.834$). In children with left USCP, no significant effects were observed (all $p>0.705$) (Figure 2D).

Reading omissions: No significant effects were observed in the entire study population (all $p>0.916$), neither in children with right USCP (all $p>0.686$) nor in children with left USCP (all $p>0.264$) (Figure 2E).

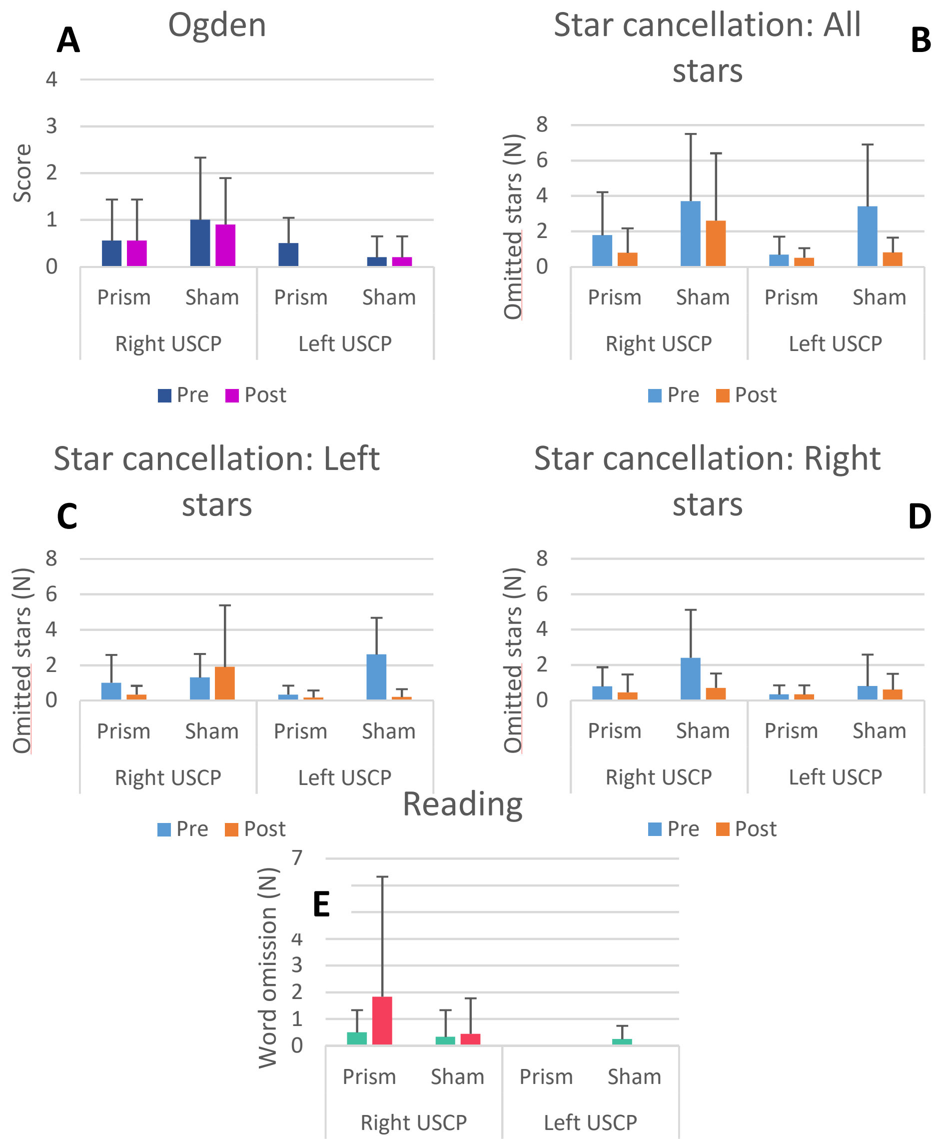

Figure 2: Performance of the children with right or left USCP in the prism and sham group before (Pre) or after (Post) the therapy in the Ogden figure copy (A) (performance as a score on 4), the star cancellation test (B-D) (performance as the number of omitted star; respectively the total number of omitted stars, the number of omitted stars on the left side and the number of omitted stars on the right side) and for the reading test (E) (performance as the number of omitted words). Bars represent the mean, and error bars represent one standard deviation.

Line bisection test: In the entire study population, no significant effects were observed (all $p>0.243$). In children with right USCP, no significant effects were observed (all $p>0.264$). In children with left USCP, two-ways ANOVA indicated a significant effect for the factor TIME $F(1;9)=14.236$; $p=0.004$. No significant effects were observed for the factor GROUP or the interaction TIME*GROUP (all $p>0.585$) (Figure 3A).

Proprioceptive pointing: No significant effects were observed in the entire study population (all $p>0.128$), neither in children with right USCP (all $p>0.602$) nor in children with left USCP (all $p>0.109$) (Figure 3B).

Visuo-proprioceptive pointing: No significant effects were observed in the entire study population (all $p>0.143$), neither in children with right USCP (all $p>0.352$) nor in children with left USCP (all $p>0.108$) (Figure 3C).

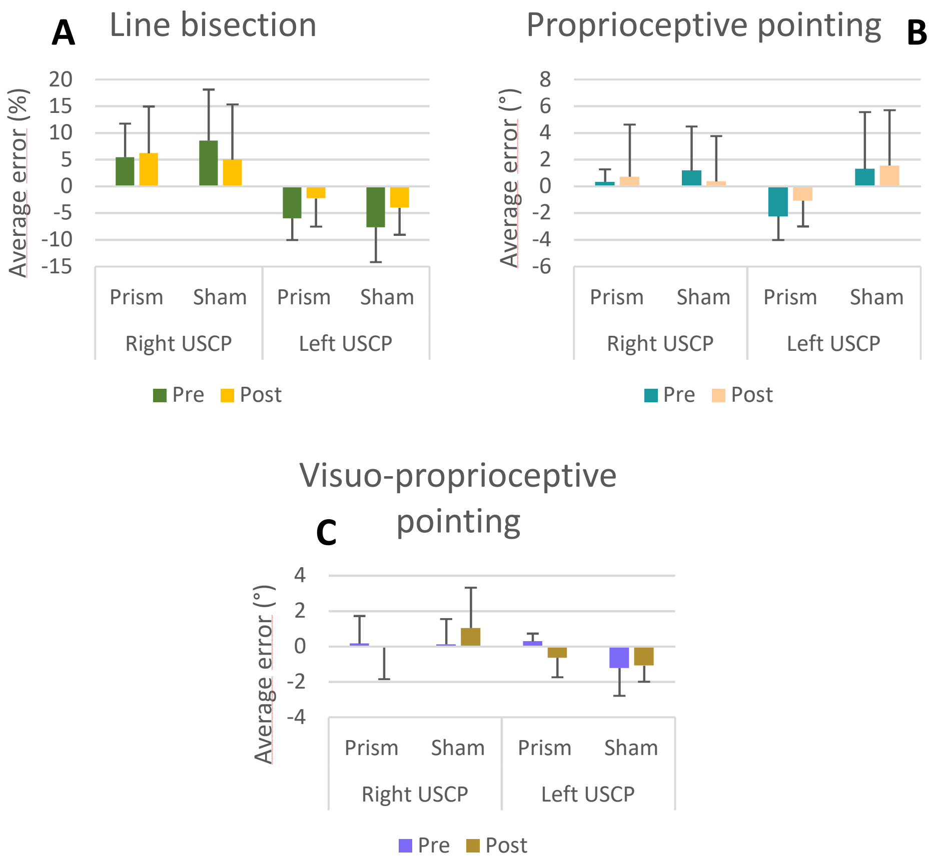

Figure 3: Performance of the children with right or left USCP in the prism and sham group before (Pre) or after (Post) the therapy in the Line bisection test (A) (performance as the average error in %), the proprioceptive pointing test (B) (performance as the average error in degree), and the visuo-proprioceptive pointing test (C) (performance as the average error in degree). Bars represent the mean and error bars represent one standard deviation.

Relationship between motor function and visuospatial assessments:
Results are presented in Table 2.

Spearman correlations were computed between the JTTHF score of the more affected UE before the intervention and the visuospatial assessments before the intervention. In the entire population, this analysis highlighted a significant correlation between the JTTHF and the Ogden figure copy test (r_s=.533, p=0.002). No other significant correlations were found in the entire population (all other p>0.18).

In children with right USCP significant correlations were observed between the JTTHF and the Ogden figure copy test (r_s=.781, p<0.001), the total number of omitted stars (r_s=.561, p=0.012), the number of left omitted stars (r_s=.469, p=0.043) and the number of right omitted stars (r_s=.494, p=0.031). No other significant correlations were found in children with right USCP (all other p>0.229). In children with left USCP, no significant correlations were observed between the JTTHF and visuospatial assessments (all p>0.157).

Spearman's correlation rho was computed between the change of JTTHF score of the more affected UE due to the intervention (computed as the difference of the scores after and before the intervention) and the change of scores of each visuospatial assessment (computed as the difference of the scores after and before the intervention). No significant correlations were observed in the entire study population (all p>0.051), in children with left USCP (all p>0.119) or in children with right USCP (all p>0.162).

Entire population		Ogden figure copy	Star cancellation			Line bisection	Proprioceptive pointing	visuo-proprioceptive pointing
			All omitted stars	Left omitted stars	Right omitted Stars			
JTTHF score of more affected U.E. pre-intervention	Spearman Rho	.533**	0.241	0.151	0.252	0.239	-0.157	-0.175
	p-value	0.002	0.199	0.426	0.18	0.204	0.407	0.355

Children with Left USCP		Ogden figure copy	Star cancellation			Line bisection	Proprioceptive pointing	visuo-proprioceptive pointing
			All omitted stars	Left omitted stars	Right omitted Stars			
JTTHF score of more affected U.E. pre-intervention	Spearman Rho	-0.12	-0.354	-0.337	-0.302	0.082	-0.458	-0.164
	p-value	0.726	0.286	0.311	0.367	0.811	0.157	0.63

Children with Right USCP		Ogden figure copy	Star cancellation			Line bisection	Proprioceptive pointing	visuo-proprioceptive pointing
			All omitted stars	Left omitted stars	Right omitted Stars			
JTTHF score of more affected U.E. pre-intervention	Spearman Rho	.781**	.561*	.469*	.494*	0.289	0.118	-0.203
	p-value	0	0.012	0.043	0.031	0.229	0.63	0.405

Table 2: Correlation between the Jebsen's score of the more affected hand before the therapy and the scores of the different visuospatial assessment before the therapy (upper table). *P-values* are reported uncorrected for multiple comparisons.

Entire population		Ogden figure copy	Star cancellation			Line bisection	Proprioceptive pointing	visuo-proprioceptive pointing
			All omitted stars	Left omitted stars	Right omitted Stars			
JTTHF Amelioration of the more affected U.E.	Spearman Rho	0.092	-0.359	-0.263	-0.064	0.176	-0.206	-0.128
	p-value	0.63	0.05	0.16	0.74	0.35	0.27	0.50

Children with Left USCP		Ogden figure copy	Star cancellation			Line bisection	Proprioceptive pointing	visuo-proprioceptive pointing
			All omitted stars	Left omitted stars	Right omitted Stars			
JTTHF Amelioration of the more affected U.E.	Spearman Rho	0.448	-0.498	-0.379	-0.438	0.018	-0.036	-0.255
	p-value	0.17	0.12	0.25	0.18	0.96	0.92	0.45

Children with Right USCP		Ogden figure copy	Star cancellation			Line bisection	Proprioceptive pointing	visuo-proprioceptive pointing
			All omitted stars	Left omitted stars	Right omitted Stars			
JTTHF Amelioration of the more affected U.E.	Spearman Rho	0.009	-0.334	-0.202	-0.009	0.174	-0.312	0.005
	p-value	0.97	0.16	0.41	0.97	0.48	0.19	0.98

Table 3: Correlation between the improvement of the Jebsen's score of the more affected hand during the therapy and the changes of the different visuospatial assessments. *P-values* are reported uncorrected for multiple comparisons.

Discussion

The aim of this study was to investigate the effectiveness of prismatic adaption rehabilitation on improving visuospatial deficits of children with USCP. Prismatic rehabilitation intervention was included in a HABIT-ILE rehabilitation summer camp. Results showed a significant influence of HABIT-ILE rehabilitation on the visuospatial attention of children with USCP. However, no differential effects of prismatic adaptation in children with USCP were observed. Significant changes due to rehabilitation therapy were found on motor function of the more affected hand (as measured by the JTTHF test), especially in children with right USCP. Correlations between motor function and visuospatial abilities before the intervention were found in children with right USCP.

Previous studies in adult stroke patients and children with brain lesions have indicated that prismatic adaption could reduce visuospatial attention deficits (Frassinetti et al., 2002; Luauté et al., 2006a; Newport and Schenk, 2012; Riquelme et al., 2015). Several factors may have influenced the lack of effects of prismatic adaptation in children with USCP. First, it is possible that the dosage of the prismatic intervention was too low in comparison with the dosage of HABIT-ILE. HABIT-ILE was delivered daily for almost 9h while prismatic adaptation lasted only 0.66h. Thus, the changes induced by prismatic adaptation may have been too small to be detected compared with the changes induced by HABIT-ILE. Second, a previous study has described an effect of prismatic adaptation on visuospatial assessments in children with USCP only in the short term (after-effect after one session) (Riquelme et al., 2015). It is possible that repetitive prismatic exposure in children with USCP is less effective than in adults stroke patients with regards to long-lasting visuospatial effects (Frassinetti et al., 2002; Luauté et al., 2006a). Third, the choice of direction of prism deviation may have interfered with the present results. From previous studies it is not clear whether the direction of prism deviation should be based on the side of UE deficit or on the side of visuospatial deficit (Torta et al., 2016). As an example, in complex regional pain syndrome visuospatial attention may be shifted either towards or away from the affected side (Sumitani et al., 2007). Visuospatial attention is not exclusively linked to the nature of the brain lesion, but also to other factors such as cognitive difficulties in body representation and behavioral effects of the relative non-use of the UE due to the motor deficit (Fontes et al., 2016; Pakula et al., 2009; Yeargin-Allsopp et al., 2008). Thus, the side of motor deficit may not always correspond to the side of spatial deficit. In the present study, the choice of direction of deviation was based on the side of UE motor deficit of each child without taking into account the results of the pre-intervention visuospatial assessments. The reason for this is that it is unclear which visuospatial assessment exactly should be used for determining the side of visuospatial deficit: body-centered proprioceptive pointing or limb-centered visuo-proprioceptive pointing or any of the other pencil-paper tests. It is possible that visuospatial effects of prismatic adaptation were intermingled at the group-level when children with same-sided motor deficits had opposite-sided visuospatial deficits before intervention. Unfortunately, the number of children included in the present study was too low to perform an *a posteriori* analysis on subgroups of children with pre-intervention visuospatial deficits on one side or the other. Also, a baseline difference was observed between the sham group and the prism group with regards to visuospatial assessments. Children in the sham group exhibited poorer performances than children in the prism group. Thus, there may have been a ceiling effect in the prism group

Though prismatic adaptation *per se* did not influence significantly visuospatial performance, the overall rehabilitation therapy with HABIT-ILE induced significant visuospatial effects in children with USCP. This unexpected result could be explained by the content of HABIT-ILE. HABIT-ILE is designed to train bimanual coordination, where children use both limbs and explore both hemispaces during therapy (Bleyenheuft and Gordon, 2014). This leads children with USCP to orient their attention and conduct action in their neglected hemispace. In this sense, HABIT-ILE is similar to other therapies such as visual scanning training (VST) or limb activation (LA) used in adults with visuospatial neglect (Antonucci et al., 1995; Luauté et al., 2006b; Priftis et al., 2013; Robertson and North, 1992). VST and LA aim at training the patient to pay and/or shift attention to his neglected side of

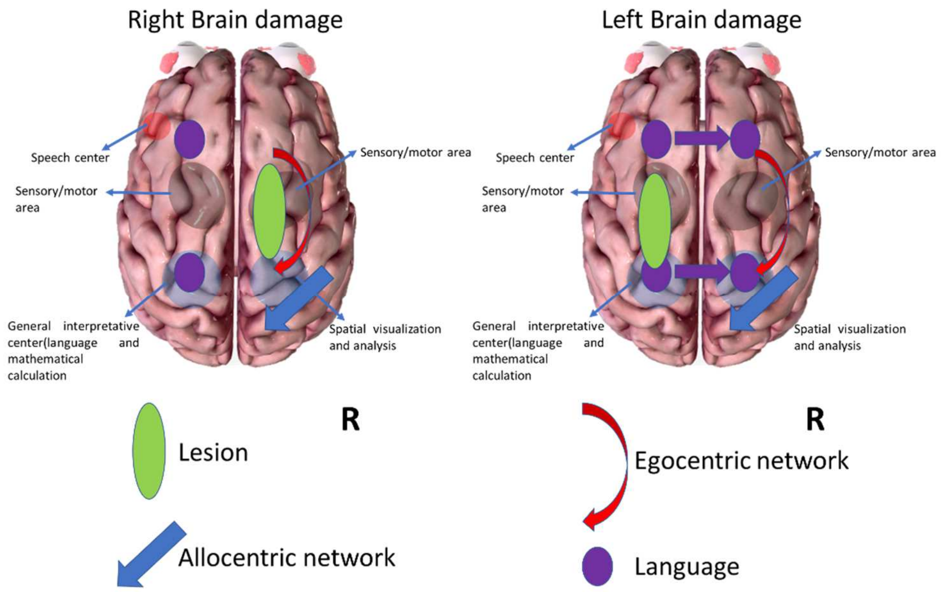

Figure 4: Illustration of brain (re)organization occurring after a right and left brain damage concerning the visuospatial and language areas.

space. VST and Limb Activation therapy have shown effectiveness in different visuospatial tasks, including the cancellation test (Antonucci et al., 1995; Luauté et al., 2006b; Priftis et al., 2013; Robertson and North, 1992). Thus, HABIT-ILE using principles applied in VST and LA could improve visuospatial attention by training the reorientation of spatial attention towards the neglected side of space. The improvement of visuospatial attention observed during HABIT-ILE either or not combined with prismatic adaptation could result from brain plasticity. Previous studies investigating the decrease of visuospatial attention deficits after specific interventions for visuospatial attention in adult stroke have suggested a role of neural plasticity and reorganization (Sturm et al., 2013; Thimm et al., 2006, 2009). HABIT-ILE also has been shown to induce neural plasticity of the motor pathways in children with USCP (Bleyenheuft et al., 2015). It appears as likely that a similar process of neural plasticity of the brain networks related to visuospatial attention could explain the improvement of visuospatial attention in children with USCP. Further imaging studies could explore this hypothesis.

Interestingly, changes in visuospatial attention were observed on different tests, depending on the lesion side. Children with right USCP improved in star cancellation – testing egocentric visuospatial attention – while children with left USCP improved in line bisection, an allocentric test of visuospatial attention. This difference might be related to the different cortical networks required to process ego and allocentric stimuli but also to differences in the process inducing a lesion in left vs right congenital brain damage.

From adult stroke patients studies, it can be suggested that while visuospatial abilities are systematically located in the right hemisphere, a dissociation in the neural structures underlying ego- and allocentric neglect exists: egocentric neglect would be related to the right fronto-parieto-temporal network while allocentric neglect to the right parieto-temporal-occipital network (Chechlacz et al., 2010).

In children with left USCP – right brain damage – the lesional mechanism inducing visuospatial deficits is generally admitted as resulting from a direct damage to areas dedicated to visuospatial abilities in the right hemisphere (Corballis, 2003). These children demonstrated in this study improvement in an allocentric test of visuospatial attention suggesting plastic changes in the parieto-temporal-occipital network but not in the fronto-parieto-temporal network responsible for processing of egocentric visuospatial attention (see illustration in Figure 4). Interestingly these children presented motor deficits on the more affected hand that were not related to visuospatial deficits. This suggests that when a direct lesion on the right hemicortex occurs, potentially affecting both the posterior part of frontal lobe – where motor cortex is located – and networks responsible for visuospatial attention, the improvements observed after intensive intervention cannot be related to the improvement of the same cortical network. It can be hypothesized that the lesion in the motor regions, inducing the motor deficits, impairs fronto-parietal connections, not allowing improvements in egocentric visuospatial attention, related to a fronto-parieto-temporal network, but allowing improvements in allocentric deficits related to a parieto-temporo-occipital network.

In children with right USCP – **left brain damage** – visuospatial deficits are likely resulting from the “crowding” of the brain area that is normally dedicated to visuospatial abilities (located in the right hemisphere) by the reorganization of language function. Indeed, language function, usually located in the left hemisphere, may develop unconventionally in the right hemisphere instead of the left following early on-set let brain inducing subsequently visuospatial deficits secondary to this reorganization (Anderson, Spencer-Smith, & Wood, 2011; Lidzba, Staudt, Wilke, & Krgeloh-Mann, 2006). Children with left brain damage of the present study improved in an egocentric test of visuospatial attention which suggests neuroplastic changes in the fronto-parieto-temporal network. Such a change is likely in this situation since the lesion is not disrupting the fronto-parietal connections, as the visuospatial abilities – though affected by the reorganization - are maintained in the unaffected hemisphere. In turn, the surprising absence of improvements in allocentric visuospatial abilities might suggest that the language relocation on the right side may disrupts the parieto-temporo-occipital network responsible for allocentric visuospatial attention. Future studies on language representation in children presenting a left brain damage may help sustaining or invalidating this hypothesis. Alternately or in combination with the disruption of different neural pathways associated to allo or egocentric visuospatial abilities due to the different lesional mechanisms, the lesion size per se might have an influence. The lesion size has been actually reported as usually larger in children with right USCP in a couple of studies (Scheck et al., 2014, 2016).

A major limitation of this study is that the beneficial effect of prismatic adaptation could be hidden behind the effect of HABIT-ILE. A future study protocol should include a higher dosage of prismatic adaptation in children with USCP.

Conclusion

Visuospatial attention in children with USCP was influenced significantly by HABIT-ILE rehabilitation intervention and not by prism adaptation. Different effects of rehabilitation were observed between children with left and right USCP which may be explained by differences in brain reorganization following an early brain lesion and by brain plasticity likely induced by HABIT-ILE. Therefore, children with left and right USCP may be investigated separately with regards to visuospatial attention and the potential (re)organization of other lateralized cognitive functions (language). Future imaging studies could clarify the brain (re)organization of visuospatial function in children with USCP before and after an intensive therapy.

Chapter VI: General Discussion

The purpose of this thesis was twofold aiming first to describe the prevalence of ego and allocentric visuospatial attention deficits in children with unilateral CP and second to investigate whether therapeutic interventions demonstrated as successful to decrease visuospatial attention deficits in adults with acquired brain lesions might be beneficial to children with congenital brain lesions. Additionally, we studied the visuospatial attention abilities of typically developing children in order to provide a reliable comparative and disentangle potential effects of pathology from development.

In the second chapter, the development of visuospatial attention in typically developing children has been investigated using widely used paper and pencil tests and normative values adapted to children have been created. Those normative values enabled us to investigate the occurrence of visuospatial attention deficits in a large sample of children with cerebral palsy, both in ego- and allocentric frames of reference (chapter III). In parallel, the relationship between visuospatial deficits and ophthalmological deficits in children with USCP has been investigated (chapter IV). Finally, upon this research, a method of rehabilitation of visuospatial deficits in children with USCP has been assessed in a randomized controlled trial (chapter V).

One of the difficulties met when investigating visuospatial attention in children is the lack of tests with normative values adapted to children. The second difficulty is that most of previous studies only assessed egocentric visuospatial attention (Laurent-Vannier et al., 2003; Lidzba et al., 2006; Trauner, 2003). In this thesis, the development of both ego and allocentric visuospatial attention was studied in typically developing children. We found a dissociation between the development of purely egocentric tests (as the star cancellation) and purely allocentric tests (as the line bisection). The latter did not show any age-related difference between 5 and 17 years old while the former did. This finding highlighted that visuospatial attention is not unitary in its development. This observation could be linked, as explained in chapter II, to a dissociation in the maturation of neural substrate related to ego- and allocentric visuospatial attention. It also highlights, as reported in previous literature, a dissociation between the neural substrate related to egocentric neglect and allocentric neglect that might be of importance in case of brain lesions: depending on the location of the lesion, isolated allo- or egocentric deficits might be observed. These results plead for carefully measuring both frames of reference in individuals with brain lesions. The normative values created in chapter II allowed us to study the prevalence of visuospatial attention deficits in children with USCP.

Chapter III, allowing to answer the first question of this thesis, highlighted that a majority of children with USCP presents visuospatial attention deficits but differences were observed in ego- and allocentric tests as well as between children with a left or a right congenital brain lesion. We highlighted that children with left USCP presented more difficulties in tests assessing egocentric neglect (star cancellation test) while children with right USCP had more difficulties in tests assessing allocentric visuospatial attention (line bisection test). These results show that the deficits are lateralized, as shown in the star cancellation test as well as in the differences existing between children with left and right USCP. Moreover, differences according to the lesions' timing have been found: children with cortico-subcortical lesions presented more visuospatial deficits than children with periventricular lesions. Cortico-subcortical lesions occur during the 3rd semester, which is less likely to allow for efficient brain reorganization (Jaspers et al., 2016).

The prevalence of visuospatial attention deficits reported in chapter III in children with USCP is very different from the prevalence encountered in adults with chronic stroke. In acute stroke, more than 50% of patients present with neglect. However most patients will recover within the first year after stroke (Bowen et al., 1999; Farnè et al., 2004; Karnath et al., 2011; Nijboer et al., 2013a). This recovery leads to a percentage of around 20 to 30 % of adult patients with neglect in chronic stroke. A second difference between children with USCP and adult stroke patients is that half of the children with left brain lesion were observed to have with visuospatial deficits, whereas in adult stroke patient, neglect following a left brain lesion is rather rare (Bowen et al., 1999). Solely studies using computerized dual tasks highlighted neglect in right-sided brain lesioned adult stroke patients while paper and pencil tests failed to highlight this discrete form of neglect (Blini et al., 2015). These observations indicate that the recovery of visuospatial attention is different according to the fact that the brain lesion occurs in a mature or immature brain. The early lesions found in children with USCP likely lead to reorganizing brain development.

Differences between right-and left brain lesioned children may be due to the localization and size of lesion as well as to the subsequent brain reorganization and development. One hypothesis which could explain the difference between children with left and right USCP is the crowding hypothesis (Anderson et al., 2011; Satz et al., 1994). Normally, the language develops in the left hemisphere while visuospatial related functions are located in the right hemisphere. One hypothesis of brain reorganization following an early lesion, the crowding hypothesis, proposes that when early cerebral lesions damage language related areas, the language will develop in the right side of the brain. Thus, undamaged areas normally dedicated to visuospatial attention are "crowded" by the development of language which impairs the development of visuospatial attention. Evidences of the crowding hypothesis have been highlighted in previous studies. Guzzetta et al. (2008) showed that children who had a left perinatal arterial stroke present a right lateralized language when the localization of the brain insults includes the Broca's area. In this study, the authors used a rhyme generation task combined with fMRI imaging to highlight language related areas. The link between language reorganization and visuospatial deficits has been highlighted in a study of Lidzba et al. (2006). The authors assessed children with a pre- or perinatally acquired left brain lesion, all the children of their sample presented cerebral palsy. The authors used a word chain task (children had to produce a word beginning by the last letter of the previous word) coupled with fMRI to assess language organization and a cancellation task to assess neglect. Their results showed a correlation between right lateralized language and the presence of neglect in children with congenitally acquired brain lesion. The crowding hypothesis could explain the differences observed between children with left and right USCP. Indeed, in children with left USCP (having a right brain lesion), visuospatial areas are directly damaged, while in children with right USCP (with a left brain lesion), visuospatial areas are not directly damaged, but less brain substrate is available subsequent to the language reorganization in the right hemisphere ("crowding"). However, this hypothesis ruled out other lesions differences which could exist between children with left and right USCP. Therefore it might be interesting in future studies to use fMRI to investigate exactly the brain areas related to visuospatial processing in children with USCP presenting a left or right brain lesion. Such studies could highlight other differences between children with USCP presenting a left or right brain lesion. Alternatively, future studies could control the lateralization of language when investigating visuospatial deficits in children with USCP. Beside the organization of visuospatial attention related brain substrate, lesion characteristics of children with left or right USCP could be different. Previous studies reported that children with right USCP present slightly larger lesions than children with left USCP (Scheck et al., 2014, 2016). Moreover, lesions of children with left and right USCP, even though being in the other hemisphere, are not all located in the same areas. Brain lesions characteristics could thus be important for differences observed in visuospatial attention deficits between children with left and right USCP and could explain their differentiated reaction to therapy. Future studies should investigate such anatomical differences when possible.

The hypothesis of language (re)organization and its relationship with the different networks implied in ego-and allocentric neglect is illustrated in Figure 1.

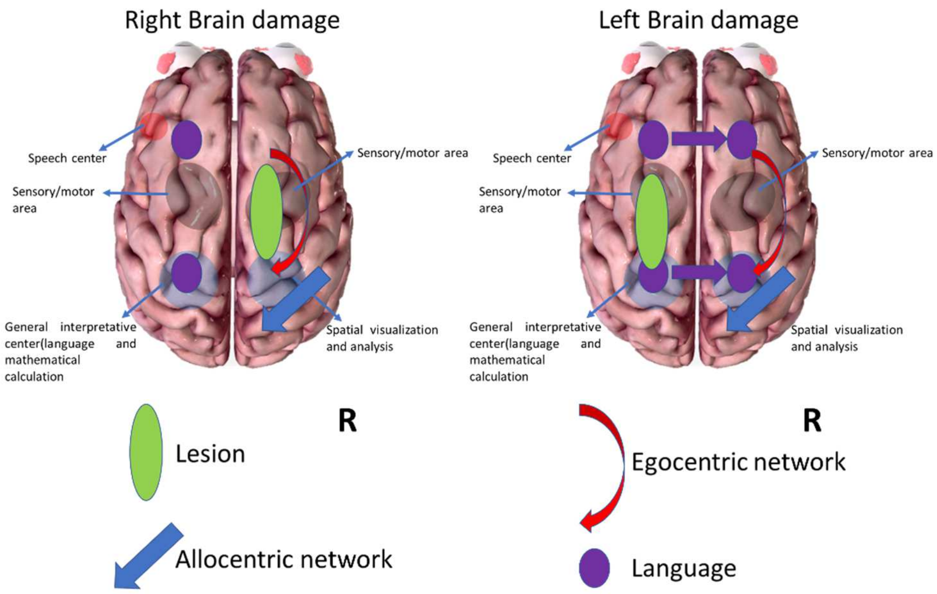

Figure 1: Illustration of brain (re)organization occurring after a right and left brain damage concerning the visuospatial and language areas.

Though it did not directly answer one of the two main questions of this thesis, we investigated whether ophthalmological deficits may influence or be mixed up with visual neglect symptoms. As described in chapter IV, a sample of children with USCP performed a thorough ophthalmological assessment (visual acuity, binocular vision assessment, strabismus assessment, visual field assessment ...) as well as a visuospatial assessment composed of the 6 tests mentioned in chapter II and III. This study highlighted that most of the children with USCP of this sample presented with a deficit of visuospatial attention, with a prevalence similar to the one reported in chapter III. More than forty percent of the children presented with binocular vision impairment or strabismus and almost one third of the sample presented a visual field defect. However, no association between visuospatial attention deficits and ophthalmological deficits was found. Visuospatial attention deficits seem thus independent of pure ophthalmological deficits in children with USCP and both should be taken into account in their rehabilitation processes. Indeed, both types of impairments are deleterious for the quality of visual feedback as well as for the accuracy of motor movements and thus for the performance in ADL.

The second question of this thesis, i.e. the rehabilitation of visuospatial attention deficits in children with USCP, was investigated in chapter V. Among the different techniques of rehabilitation, prismatic adaptation (PA) has been reported as one of the most effective to reduce neglect symptoms in the short and long term as well as to increase the performance of ADL in adult stroke patients. Moreover, prismatic rehabilitation has been shown feasible in children with cerebral palsy in another study (Riquelme et al., 2015). Therefore we designed a randomized control trial studying the effectiveness of PA to treat visuospatial attention deficits in children with USCP. In this trial, children with USCP received either prismatic adaption or treatment with sham glasses while following a two weeks HABIT-ILE intensive motor therapy. No effect of prismatic adaption was found though a general effect of the intensive motor rehabilitation (HABIT-ILE) was observed on visuospatial attention. Children in both intervention groups (prism and sham) showed an improvement of visuospatial attention during rehabilitation.

An explanation for the presence of this effect of HABIT-ILE is the similarity between some components of HABIT-ILE and of rehabilitation techniques of visual neglect as visual scanning training (VST) and limb activation (LA) (Antonucci et al., 1995; Luauté et al., 2006b; Priftis et al., 2013; Robertson and North, 1992). In VST, patients are trained to visually scan their neglected hemispace for stimuli, while in LA, patients are asked to use their limb located on their neglected side to carry on action in both hemispaces. These characteristics are found in HABIT-ILE in which children use both limbs in a coordinated fashion to carry out action in both hemispaces (Bleyenheuft and Gordon, 2014). These two tests assess ego- or allocentric visuospatial attention underlining an effect of HABIT-ILE on both frames of reference of visuospatial attention. This reduction of visuospatial attention deficits in children with USCP following intensive motor therapies could also be beneficial in terms of improvement of visual feedback and thus indirectly on their performance in activities of daily living (ADL). This effect of HABIT-ILE on the results of visuospatial attention tests highlights the close relationship between the visuospatial abilities and the motor function, as observed during goal-directed tasks (Chatterjee, 2003). In this way, we can hypothesize that a motor disorder during development may impact upon visuospatial attention. Indeed, children presenting spastic diplegia associated with prematurity show an impairment in the orienting task (Craft et al., 1994). In addition, walking typically developing children have better spatial abilities than non-walker age-matched peers (Kermoian and Campos, 1988). This suggests that the relationship between motor and visuospatial abilities is probably due to the environment interaction needed to develop the spatial abilities.

The unexpected absence of effect of prismatic adaptation (PA) could be explained by different hypotheses. One explanation of the lack of effect of PA could be the low intensity of PA. Frassinetti et al. (2002) reported long-lasting improvement of neglect using a similar intensity of PA, in the treatment of visuospatial attention deficits in adult patients. The intensity used by the authors was of 2 sessions of 20 minutes per days during 2 working weeks for a total of 20 sessions which is similar to the intensity used in chapter V. Similar improvement in neglect symptoms of adults patients also has been reported with 10 sessions of 20 minutes of PA administrated over the course of two weeks (Serino et al., 2007). Moreover, lasting effects of PA have also been highlighted after only one session (Pisella et al., 2002). It is unlikely that the intensity of PA treatment used in chapter V was too low as even studies investigating the effect of PA using lower dosage intensity reported results. Alternatively, the effect of the intensive motor therapy could hide the potential effect of PA. This could be due to the time ratio of both interventions (a little more than 6 hours for PA in comparison of 90 hours for HABIT-ILE therapy). Another explanation for the lack of observable effects of PA in children with USCP in chapter V is that the after effect previously observed by Riquelme et al. (2015) is only transient and does not produce lasting effects in children with USCP. It is possible that the effects of PA sessions are not additive in children with USCP and that therefore the after effect may fade out more rapidly than in adult patients. In the study reported in chapter V, children with USCP were assessed almost a day after their last PA session. To control for this problem, effects of PA could be measured at different time points after the session by using a target pointing or straight-ahead pointing task. It should also be noted that a previous study reported a dissociation between evolution of performance in straight-ahead pointing and line bisection task after PA. In this study investigating the effect of PA on two patients with neglect, Pisella et al. (2002) showed that subsequently to PA, one patient improved her performance in the pointing task while the other improved her performance in the line bisection task. These latter observations indicate that not all patients with neglect respond in the same way to PA. A similar dissociation between changes in pointing task and line bisection judgement task has been observed in healthy adults after PA with rightwards or leftwards deviating prisms. Schintu et al. (2014) showed that healthy participants with leftwards deviating prisms showed a deviation to the right in the pointing task as well as a reduction of error in the line bisection judgement task after PA while participants receiving rightwards deviating PA showed an error to the left in the pointing task but no reduction of error in the line bisection judgement task. These dissociative effects may be another explanation for the lack of effect of prismatic adaption in children with USCP. In chapter V, the sample included children with a left (right USCP) or right (left USCP) brain lesion which received PA with respectively right or left deviating prisms. It is possible that for some children the side of deviation of the prisms was not the correct one to create a long lasting after effect. One can speculate that PA could have been more effective if the side of prisms deviation had been chosen in accordance with the deviation shown at baseline by children in a pointing task or with the side of neglect (upon clinical observation). More research is needed to conclude on this issue as Luauté et al. (2012) reported that prisms inducing a left deviation did not improve the performance of in adult neglect. Thus, leftwards deviating prisms could be ineffective in children with USCP presenting visuospatial attention deficits in the left hemispace. Different responses in children were related to the differential effects of PA in function of the side and characteristics of brain lesion. Such differences between children with left and right USCP have been also reported in chapter III.

From a general point of view, vision and visuospatial attention play a central role in ADL (Gonzalez and Niechwiej-Szwedo, 2016; Mlinac and Feng, 2016; Nataraj et al., 2014; Nijboer et al., 2013b; Nys et al., 2005). Without the notification of visual stimuli, the surrounding environment might be extremely dangerous in various situations (e.g. not noticing a car while crossing a road). Besides the safety issues related to visuospatial attention, this modality seems crucial to plan and update the motor command allowing any human being to interact with his/her environment (Coulthard et al., 2006; Gritsenko and Kalaska, 2010; Gritsenko et al., 2009; Scott et al., 2015). Every movement is performed based on internal models, i.e. neural mechanisms that can estimate the input/output characteristics, or their inverses, of the motor apparatus (Kawato, 1999). Internal models include both forward internal models that predict sensory consequences from efference copies of issued motor commands and inverse internal models that calculate necessary feedforward motor commands from desired trajectory information.

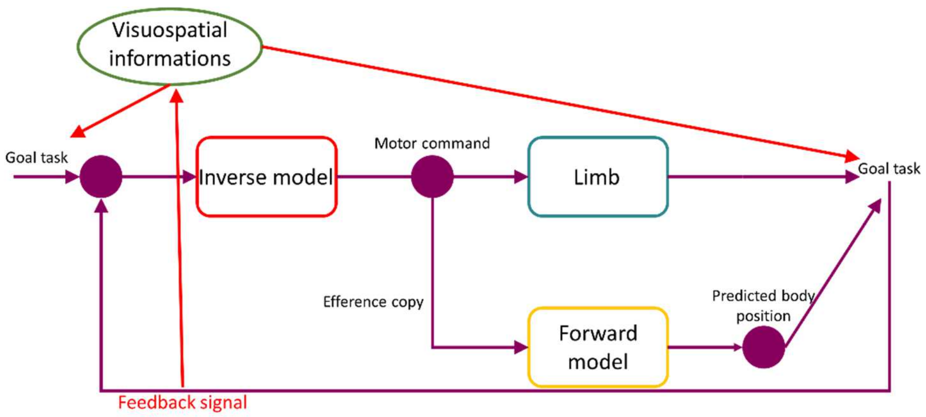

Figure 2: Internal model for motor action adapted from Kawato (1999). Visuospatial informations are needed to compute the desired trajectory, to compare the desired task with the realized task, using information from the feedback signal.

These internal models require both an ability to produce a forward model (based on previous experience and on visual information) and an ability to estimate a priori the feedback that will result from the desired movement (inverse model) allowing to compare the actual sensory feedbacks with the prediction to update the motor command if needed. Vision and visuospatial attention will be crucial in this process both for the building of internal models to create a motor command adapted to the characteristics of the object manipulated and to the task performed, but also in the process of feedback loops allowing to adapt the model. In many occasion during manipulation in everyday life visual feedback is actually replaced by perception (tactile and proprioceptive feedbacks) (Franklin et al., 2007; Sarlegna and Sainburg, 2009). This is for instance highlighted when observing the gradual learning of a violinist whose fingers position on the fingerboard will be first regulated by visual feedback and will gradually rely more on proprioceptive and auditory feedbacks. Studies on manipulative forces demonstrated that in more basic conditions such as gripping and lifting a simple object, the forces applied to the object are regulated by both relying on visual feedbacks, as demonstrated by the importance of visual cues in the forces exerted on an objects (Gordon et al., 1991), and on tactile/proprioceptive information as highlighted when the grip surfaces of an object are modified (more or less slippery) without visual cues (Forssberg et al., 1995), as well as during anaesthesia of sensory afferences preventing a correct adaptation of manipulative forces (Nowak et al., 2002). In case report of a deafferented patient, it has been shown that the complete absence of tactile/proprioceptive feedback can be compensated by vision to perform successful attempts of manipulation (Ghez et al., 1995; Messier et al., 2003; Nowak and Hermsdörfer, 2006). In this case, the patient even described visual strategies related to the speed of her arm when lifting an object to define the weight of the object (Nowak and Hermsdörfer, 2006).

A deficit in visuospatial attention is likely to have consequences on the ability to manipulate objects. It sounds relevant to wonder whether part of a deficit in functional abilities may be related to the visuo-spatial deficit and whether it can be treated.

Indeed, previous studies have linked visuospatial neglect to impaired motor control as well as reaching and grasping deficits. In a review about motor control in neglect patients, Coulthard et al. (2006) reported that neglect patients present longer movement execution time, as well as disrupted trajectories during reaching. The authors reported that several previous studies highlighted the lengthened movement execution towards contralateral and ipsilateral targets. The subsequent analysis of movement execution in patients with visuospatial neglect showed an increase in the time of deceleration. Regarding these results, the authors suggested that patients with visuospatial neglect rely more on terminal visual guidance when reaching towards objects. Other studies investigated the movement paths of patients with neglect during a reaching task in three conditions of visual feedback (Jackson et al., 2000). The three conditions of visual feedback were full vision condition, vision of the arm but not of the target (the target was defined through proprioception) and with no vision. When compared to the movement path made by healthy participants, the authors found that patients with neglect presented an increase curvature of their movement in the full vision condition compared to the no-vision condition (Jackson et al., 2000). Differences in movement were also observed in a study of Farnè et al. (2003) in which healthy participants, and right brain damaged patients with or without neglect, had to point to illuminated targets presented either in front of them, on their left or on their right. Their experiment included two conditions, one in which the same target was illuminated during the trials and a second one in which the illuminated target changed once participants initiated their movements. In the second condition, participants had to re-orient their movement towards the new target (perturbed condition). This study highlighted that in comparison to patients without neglect, patients with neglect in the perturbed condition, showed smaller acceleration peak and longer time to maximum grip aperture. Patients of both kinds also showed diminished movement speed compared to healthy participants. Another study by Semrau et al. (2015) also highlighted impaired kinesthesia in patients presenting neglect. In their study, the authors asked control patients, stroke patients and stroke patients presenting neglect to reproduce the movement felt with one arm with the other arm while not having visual feedback. They showed that compared to controls and stroke patients without neglect, a higher percentage of patients with neglect presented kinesthetic impairments highlighting a relation between the presence of neglect and kinesthetic deficits. These studies, showed that neglect patients have difficulties to interpret and properly integrate visual and kinesthetic cues which lead to impaired movement production. Taking into account these observations and the internal model theory, it seems that in neglect patients it is mostly the feedback loop used to update the motor command and the forward model that would be impaired.

This question of whether visuospatial deficits may impact motor function is relevant for patients with a visuospatial deficit as their main impairment but could become even more crucial in patients where both perception/tactile abilities and visual feedbacks are affected since vision won't be able to compensate for the absence of tactile/proprioceptive feedback. Most children with USCP encounter deficits in tactile/proprioceptive function since up to 90% of these children present a sensory dysfunction on the most affected upper extremity (Bleyenheuft & Gordon, 2013). These dysfunctions have an influence on their ability to develop adapted motor commands for the paretic upper extremity (Bleyenheuft and Gordon, 2013). Therefore their ability to plan a motor command may rely even more on visual feedback. As exposed previously, inverse and forward models, internal representation of the movement and its consequences, are learned based on experience and on movement feedback information. In the case of children with USCP, the presence of sensory and visuospatial deficits is likely to alter the acquisition of accurate inverse models. This is very different from adult stroke patients who already developed most of their inverse models. Most children with USCP still have to develop theirs as part of motor development and training (Kawato, 1999; Wolpert and Flanagan, 2010) (Figure 2). As a consequence, the presence of visuospatial attention deficits would increase and delay their motor learning impairments. The presence of visuospatial attention deficits is also likely to impair the selection of a correct module, as proposed by Kawato et al. (1999) or to impair the shifting to another one if needed, when producing motor actions. In addition, children with USCP, as adult stroke patients, are likely to present altered feedback information because of the presence of visuospatial attention deficits which may lead to altered movements' execution. This was exposed above in the studies investigating motor movement in adult stroke patients with neglect.

Finally, with regards to the previous observations, one could wonder how motor abilities influence visuospatial attention abilities. In this thesis, we observed that visuospatial attention deficits could be treated by intensive motor therapy as described in chapter V. Also, the importance of accurate feedback (both somatosensory and visuospatial) during motor learning was discussed. Previous studies reported the importance of the ability of exploring one's surroundings (to walk) to develop visuospatial attention (Kermoian and Campos, 1988). Studies on the representation of space reported that motor restriction could change the representation of the peripersonal space. The representation of the peripersonal space has been shown as a dynamic entity partly dependent upon the motor capacity, restricted use of limbs and use of tools. All these findings suggest an active role of motor development and motor actions in the development of visuospatial attention abilities.

On the other hand, theories on the internal model for motor action highlighted the importance of visual and visuospatial information to 1) develop accurate inverse model; 2) to choose the correct inverse model prior to an action; 3) to produce an accurate forward model; 4) to have a reliable feedback signal and to correctly integrate it (Figure 2) (Franklin et al., 2007, 2012; Kawato, 1999; Wolpert and Flanagan, 2010). The quality of feedback information (visual, visuospatial and sensorimotor) is important in order to update the forward model and produce accurate online motor control. The deleterious effect of altered visuospatial abilities on motor action was reported repeatedly in adult stroke patients with neglect.

Children with USCP present with an initial motor deficit. It is thus important to question the exact relationship between the development of motor and visuospatial abilities in order to develop and adapt rehabilitation strategies. Could the initial motor deficits alter the development of visuospatial abilities? May visuospatial attention deficits prevent motor development and increase the learned non-use of the more affected UE in children with USCP? With regards to previous literature and to the results of this thesis, we hypothesize that motor deficits influence the development of visuospatial attention abilities and vice-versa.

General conclusion

The first question of this thesis concerned the prevalence of visuospatial attention deficits in children with USCP. On that matter, we have shown that visuospatial deficits are present in more than 50% of children with USCP both in the ego- and allocentric frame of reference and that these deficits are independent from ophthalmological impairments. This thesis highlighted in addition differences between children with right and left brain lesions, as well as between ego and allocentric reference frames, suggesting that though it seems important to develop therapeutic interventions, one strategy may not fit for all children.

The question of the effectiveness of a therapeutic intervention for children in CP was investigated using prism adaptation during an intensive motor skill learning based intervention. Though prism adaptation per say did not induce an improvement in visuospatial attention, HABIT-ILE did. This intervention, based on motor skill learning, requires a continuous bimanual manipulation associated to postural and/or locomotor stimulations. The improvements observed in visuospatial attention –both in ego and allocentric tests – over the 90 hours of intervention suggest that interventions presenting these characteristics of intensity, shaping, with a high attention level constantly directed to the peripersonal space are likely to induce changes not only in motor function but also in visuospatial abilities. It is still unknown however which components of this therapy induced the change and whether improvements might be enhanced if intervention is better targeted to fit the characteristics of each child. Children with USCP are generally presenting significant improvements in motor function and functional abilities in the course of a HABIT-ILE intervention (Bleyenheuft et al., 2015). It is also unknown which amount of this motor change might be actually related to the improvement in visuospatial abilities, allowing an access to better information and feedbacks to form and update motor programs.

The results of this thesis strongly suggest the interest of assessing more systematically visuospatial deficits in children with USCP. In addition, the influence of motor skill learning based interventions on visuospatial deficits requires further investigation. Is this phenomenon observed in HABIT-ILE generated by other intensive motor interventions? Could constraint-induced movement therapy or Hand-arm bimanual intensive therapy (HABIT, without a LE component) induce the same changes? At which dosage is the effect observed and are the changes similar for all children or might there be some differences depending on brain lesion side, brain lesion size or brain lesion timing or even the nature of the visuospatial deficit? Could the potential amount of changes in visuospatial abilities be age dependent and have specific windows of opportunity? What is the exact relationship between visuospatial attention development and motor development?

Though this thesis offers a first answer to the possibility of improving visuospatial abilities in children with USCP, suggesting the interest of intensive motor skill learning based interventions, it raises many new questions that should be answered to better understand and treat visuospatial attention deficits in children with cerebral palsy.

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Appendix

Test	Variable	Age group (yrs)	Subjects (n=)	Mean	Standard Deviation	95%-confidence interval
Line bisection	average error (%)	5	9	3.58	8.964	-14.35 - 21.51
		6	11	-3.08	3.970	-11.02 - 4.86
		7	14	-2.30	3.905	-10.11 - 5.51
		8	12	-2.56	4.784	-12.13 - 7.01
		9	14	-1.24	3.164	-7.56 - 5.09
		10	13	-2.83	3.934	-10.7 - 5.04
		11	8	-3.26	2.877	-9.01 - 2.5
		12	13	-0.10	3.672	-7.44 - 7.25
		13	17	-0.89	2.738	-6.36 - 4.59
		14	13	-0.81	3.155	-7.12 - 5.5
		15	12	0.20	2.223	-4.25 - 4.64
		16	12	-0.16	3.878	-7.91 - 7.6
		17+	11	-2.19	3.221	-8.63 - 4.26
Proprioceptive pointing	average	5	9	1.97	3.315	-4.66 - 8.6
		6	11	-2.27	5.011	-12.29 - 7.75
		7	14	0.61	6.030	-11.45 - 12.67
		8	12	-0.77	4.060	-8.89 - 7.35
		9	14	-1.64	2.425	-6.49 - 3.21
		10	13	-1.87	2.899	-7.66 - 3.93
		11	8	-2.13	3.265	-8.66 - 4.41
		12	13	0.46	3.087	-5.71 - 6.64
		13	17	0.68	2.517	-4.36 - 5.71
		14	13	-0.67	2.829	-6.33 - 4.99
		15	12	0.31	2.012	-3.71 - 4.34
		16	12	-0.63	2.149	-4.92 - 3.67
		17+	11	0.23	2.951	-5.67 - 6.13

Appendix Table 1 A: Pediatric reference values by age group for the variables with a Gaussian distribution.

Test	Variable	Age group (yrs)	Subjects (n=)	Mean	Standard Deviation	95%-confidence interval
Visuo-proprioceptive pointing	average error (°)	5	8	0.17	2.217	-4.27 - 4.6
		6	11	0.45	1.354	-2.25 - 3.16
		7	13	-0.02	1.240	-2.5 - 2.46
		8	12	0.83	1.161	-1.49 - 3.15
		9	13	0.40	0.738	-1.07 - 1.88
		10	13	-0.15	0.873	-1.89 - 1.6
		11	8	0.22	0.754	-1.28 - 1.73
		12	13	0.29	1.111	-1.93 - 2.51
		13	17	0.46	0.916	-1.37 - 2.29
		14	13	0.06	0.870	-1.67 - 1.8
		15	12	0.02	0.494	-0.97 - 1.01
		16	12	-0.24	0.601	-1.44 - 0.96
		17+	11	0.11	0.696	-1.28 - 1.5
	right target error (°)	5	8	-1.67	1.886	-5.44 - 2.1
		6	11	-0.70	1.912	-4.52 - 3.13
		7	13	-1.29	1.844	-4.97 - 2.4
		8	12	-0.46	2.500	-5.46 - 4.54
		9	13	-0.43	1.165	-2.76 - 1.9
		10	13	-1.69	1.023	-3.74 - 0.35
		11	8	-1.08	1.707	-4.5 - 2.33
		12	13	0.26	1.973	-3.69 - 4.2
		13	17	0.24	1.928	-3.62 - 4.09
		14	13	-0.56	1.595	-3.75 - 2.63
		15	12	-0.51	0.601	-1.72 - 0.69
		16	12	-0.47	1.403	-3.28 - 2.33
		17+	11	0.09	1.156	-2.22 - 2.4
	central target error (°)	5	8	0.42	2.158	-3.9 - 4.73
		6	11	1.03	1.760	-2.49 - 4.55
		7	13	0.62	2.132	-3.64 - 4.88
		8	12	0.58	0.889	-1.19 - 2.36
		9	13	0.93	1.675	-2.42 - 4.28
		10	13	-0.26	0.992	-2.24 - 1.73
		11	8	0.17	1.024	-1.88 - 2.21
		12	13	0.10	1.125	-2.15 - 2.35
		13	17	0.51	1.259	-2.01 - 3.03
		14	13	0.05	0.792	-1.53 - 1.63
		15	12	-0.11	0.845	-1.8 - 1.58
		16	12	-0.44	0.499	-1.44 - 0.55
		17+	11	-0.24	0.858	-1.96 - 1.47
	left target error (°)	5	8	1.75	3.156	-4.56 - 8.06
		6	11	1.03	1.906	-2.78 - 4.84
		7	13	1.67	2.816	-3.97 - 7.3
		8	12	2.36	1.494	-0.63 - 5.35
		9	13	1.64	2.073	-2.5 - 5.79
		10	13	1.51	1.751	-1.99 - 5.02
		11	8	1.58	1.571	-1.56 - 4.73
		12	13	0.51	1.778	-3.04 - 4.07
		13	17	0.63	1.092	-1.56 - 2.81
		14	13	0.71	1.313	-1.92 - 3.33
		15	12	0.69	1.176	-1.66 - 3.05
		16	12	0.19	0.834	-1.47 - 1.86
		17+	11	0.48	0.970	-1.46 - 2.43

Appendix Table 1 B: Pediatric reference values by age group for the variables with a Gaussian distribution.

Test	Variable	Age group (yrs)	Subjects (n =)	Median	Interquartile range	25th -95th Percentile
Star cancellation	all stars omission (n =)	5	9	3.00	4.50	0.5 - 9
		6	11	1.00	4.00	0 - 8
		7	14	1.00	2.50	0 - 9
		8	12	2.00	3.75	0.25 - 9
		9	14	1.00	2.25	0 - 4
		10	13	1.00	2.00	0 - 4
		11	8	0.00	0.00	0 - 1
		12	13	0.00	1.00	0 - 1
		13	17	0.00	1.00	0 - 3
		14	13	0.00	0.00	0 - 2
		15	12	0.00	0.00	0 - 0
		16	12	0.00	0.00	0 - 0
		17+	11	0.00	0.00	0 - 4
	left stars omission (n=)	5	9	0.00	3.50	0 - 9
		6	11	1.00	3.00	0 - 4
		7	14	1.00	2.25	0 - 5
		8	12	1.00	2.00	0 - 4
		9	14	0.00	0.25	0 - 2
		10	13	0.00	1.50	0 - 4
		11	8	0.00	0.00	0 - 1
		12	13	0.00	0.00	0 - 0
		13	17	0.00	0.50	0 - 3
		14	13	0.00	0.00	0 - 0
		15	12	0.00	0.00	0 - 0
		16	12	0.00	0.00	0 - 0
		17+	11	0.00	0.00	0 - 4
	right stars omission (n=)	5	9	1.00	1.50	0 - 4
		6	11	0.00	1.00	0 - 4
		7	14	0.00	0.00	0 - 4
		8	12	1.00	2.75	0 - 5
		9	14	0.50	1.25	0 - 4
		10	13	0.00	1.00	0 - 2
		11	8	0.00	0.00	0 - 0
		12	13	0.00	1.00	0 - 1
		13	17	0.00	0.00	0 - 1
		14	13	0.00	0.00	0 - 2
		15	12	0.00	0.00	0 - 0
		16	12	0.00	0.00	0 - 0
		17+	11	0.00	0.00	0 - 0
	time (s)	5	9	174.00	72.00	135 - 222
		6	11	100.00	15.50	93.5 - 140
		7	14	74.00	16.75	63.25 - 113
		8	12	75.00	28.00	57.5 - 91
		9	14	64.50	30.00	48 - 89
		10	13	55.00	25.00	44 - 103
		11	8	44.50	42.00	44 - 111
		12	13	47.00	8.00	42.5 - 57
		13	17	40.00	12.50	35 - 125
		14	13	39.00	11.50	32.5 - 61
		15	12	38.50	8.25	36 - 46
		16	12	42.00	13.25	36.25 - 91
		17+	11	34.00	8.00	32 - 58

Appendix Table 2 A: Pediatric reference values by age group, for the variables with a non-Gaussian distribution.

Test	Variable	Age group (yrs)	Subjects (n =)	Median	Interquartile range	25th -95th Percentile
Ogden figure copy	score	5	9	1.00	2.00	0 - 2
		6	11	0.00	0.00	0 – 2
		7	14	0.00	0.25	0 – 1
		8	12	0.00	0.75	0 – 1
		9	14	0.00	0.00	0 – 0
		10	13	0.00	0.00	0 – 0
		11	8	0.00	0.00	0 – 0
		12	13	0.00	0.00	0 - 0
		13	17	0.00	0.00	0 - 1
		14	13	0.00	0.00	0 - 0
		15	12	0.00	0.00	0 - 0
		16	12	0.00	0.00	0 - 0
		17+	11	0.00	0.00	0 - 0
	time (s)	5	9	212.00	96.50	164 - 309
		6	11	128.00	47.00	97 - 173
		7	14	103.00	33.50	93.5 - 167
		8	12	82.50	36.75	73.25 - 175
		9	14	93.00	32.75	75 - 180
		10	13	79.00	42.00	72 - 176
		11	8	93.00	58.00	72 - 173
		12	13	65.00	26.00	50.5 - 130
		13	17	68.00	17.00	60 - 102
		14	13	52.00	19.00	40 - 94
		15	12	53.50	30.00	37.25 - 95
		16	12	60.00	26.75	43.25 - 101
		17+	11	60.00	25.00	38 - 65
Reading	word omission (n=)	7	14	0.00	0.00	0 - 0
		8	12	0.00	0.00	0 - 1
		9	14	0.00	0.00	0 - 1
		10	13	0.00	1.00	0 - 1
		11	8	0.00	1.00	0 - 1
		12	13	0.00	1.00	0 - 1
		13	17	0.00	0.00	0 - 1
		14	13	0.00	1.00	0 - 1
		15	12	0.00	0.00	0 - 1
		16	12	0.00	1.00	0 - 1
		17+	11	0.00	0.00	0 - 1
	word substitution (n=)	7	14	2.00	2.50	0 - 4
		8	12	0.00	1.00	0 - 2
		9	14	0.00	0.00	0 - 1
		10	13	0.00	1.00	0 - 2
		11	8	0.00	0.00	0 - 1
		12	13	0.00	0.00	0 - 1
		13	17	0.00	0.00	0 - 0
		14	13	0.00	0.00	0 - 1
		15	12	0.00	0.00	0 - 1
		16	12	0.00	0.00	0 - 0
		17+	11	0.00	0.00	0 - 1
	time (s)	7	14	85.50	94.00	58 - 195
		8	12	50.50	29.25	35.5 - 93
		9	14	43.00	13.75	37.5 - 68
		10	13	38.00	15.50	31 - 106
		11	8	31.50	15.25	31 - 49
		12	13	26.00	4.50	24.5 - 32
		13	17	25.00	5.50	22 - 34
		14	13	23.00	8.00	21.5 - 38
		15	12	21.00	3.50	19.25 - 30
		16	12	21.50	3.25	20.25 - 25
		17+	11	23.00	5.00	20 - 29