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Spontaneous improvement in oculomotor function of children with cerebral palsy

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ABSTRACT

Eye movements are essential to get a clear vision of moving objects. In the present study, we assessed quantitatively the oculomotor deficits of children with cerebral palsy (CP). We recorded eye movements of 51 children with cerebral palsy (aged 5–16 years) with relatively mild motor impairment and compared their performance with age-matched control and premature children. Overall eye movements of children with CP are unexpectedly close to those of controls even though some oculomotor parameters are biased by the side of hemiplegia. Importantly, the difference in performance between children with CP and controls decreases with age, demonstrating that the oculomotor function of children with CP develops as fast as or even faster than controls for some visual tracking parameters. That is, oculomotor function spontaneously improves over the course of childhood. This evolution highlights the ability of lesioned brain of children with CP to compensate for impaired motor function beyond what would be achieved by normal development on its own.

1. Introduction

With about 2–4 cases out of every 1000 children, cerebral palsy (CP) which is a disorder of movement and posture due to a lesion of the fetal or infant brain is the most common cause of motor disability in childhood (Rosen & Dickinson, 1992; Yeargin-Allsopp et al., 2008). Children with cerebral palsy suffer from several disorders of movement and posture. Impairment of sensation is also commonly encountered by children with CP.

Vision is especially important for children with CP. Indeed, these children tend to rely more on visual feedback than typically developing children (Gordon & Duff, 1999; Valvano & Newell, 2008). Beyond that, visual problems may interfere with motor learning and may be responsible for some of their impairment in manual and locomotor abilities (Adelson & Fraiberg, 1974; Bigelow, 1992; Lee & Aronson, 1974).

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Visual deficits can arise from either the perceptual or the motor deficits. Perceptual deficits are very frequent in children with CP as only 20% of them have normal vision (Black, 1982). The most common perceptual deficits for these children are refractive errors, reduced visual acuity and strabismus (in more than 50% of children with CP) (Barca, Cappelli, Di Giulio, Staccioli, & Castelli, 2010; Black, 1980, 1982; Fazzi et al., 2007; Kozeis et al., 2007; Stiers et al., 2002).

Beyond perceptual deficits, oculomotor deficits can also have a role in visual disabilities of children with CP. Nystagmus is the most frequent motor deficit (Barca et al., 2010; Black, 1980; Kozeis et al., 2007; Stiers et al., 2002) and certainly reduces the quality of the perceived visual information. However, accurate eye movements are also crucial to get a clear vision of the environment. Smooth pursuit and saccadic eye movements (Krauzlis, 2004; Orban de Xivry & Lefèvre, 2007) are used to stabilize the image of selected objects on the fovea (region of the retina with the highest acuity). Clinicians can gain valuable information from quantitative studies of eye movements. They provide important information about the origin or the progression of specific diseases (Leigh & Zee, 2006) and provide a window into brain functions (Ramat, Leigh, Zee, & Optican, 2007). For instance, abnormal volitional saccades (e.g. increased latency and increased error rate during an anti-saccade task) provide an accurate biomarker for presymptomatic and early stage Huntington disease patients (Blekher et al., 2006). In particular, eye movement studies in children give valuable information about the development of specific brain functions (Luna, Velanova, & Geier, 2008). In children with cerebral palsy, the use of eye movement recordings could bypass the use of affected limbs in the characterization of their development. However, despite their importance in vision, very few studies tackled the possible deficit in smooth pursuit and saccades (two types of orienting eye movements) of children with CP. To fill this gap, the goal of this study is to provide high-quality data on smooth pursuit eye movements in a large cohort of children with CP.

Many previous studies on oculomotor function in children with CP relied on an orthoptist or on video based examination to score the oculomotor function (Barca et al., 2010; Fazzi et al., 2012; Jackson, Castleberry, Galli, & Arnoldi, 2006; Mayberry & Gilligan, 1985; Palma da Cunha Matta et al., 2008; Salati, Borgatti, Giammari, & Jacobson, 2002). In addition to data quality concerns, these studies may not allow interpreting adequately common oculomotor behaviors. For instance, smooth pursuit may be qualified as impaired when interspersed by saccades (Salati et al., 2002), even though it is well known that both smooth pursuit and saccades are typically used to follow moving targets (de Brouwer, Yuksel, Blohm, Missal, & Lefèvre, 2002; Ego, Orban de Xivry, Nassogne, Yüksel, & Lefèvre, 2013).

A few studies quantitatively analyzed eye movements in children with CP. However, most of these earlier studies were based on a very small cohort of children (4–6 children or adults) (Coltellaro, LeGare, & Terdiman, 1995; Horínek et al., 2008; Lee, LeGare, & Zhang, 1995; Zhang, LeGare, & Lee, 1998). This number of subjects is particularly low when taking into account the variety of severity and diversity of deficits characterizing children with CP. Such small cohort of patients with CP does not allow assessing the role of age on oculomotor function in these children while it is known that both saccade and pursuit performance are modulated by age in typically developing children (Accardo, Pensiero, Da Pozzo, & Perissutti, 1992; Accardo, Pensiero, Da Pozzo, & Perissutti, 1995; Ego et al., 2013; Fukushima, Hatta, & Fukushima, 2000; Katsanis, Iacono, & Harris, 1998; Luna et al., 2008; Ross, Radant, & Hommer, 1993; Salman, Sharpe, Eizenman, et al., 2006; Salman, Sharpe, Lillakas, Dennis, & Steinbach, 2006) and deteriorate with age in adults (Irving, Steinbach, Lillakas, Babu, & Hutchings, 2006; Morrow & Sharpe, 1993).

Finally, we identified two studies that assessed oculomotor function in slightly larger cohorts of children with CP (~15 children). The first study focused on saccadic eye movements in 16 children with CP aged 6–13 years (Katayama & Tamas, 1987) but had no control group of typically developing children. In contrast, the second study investigated in details the development of eye movements in 15 children with CP (from 6 to 16 years old) and in typically developing children and found small differences in smooth pursuit performance across groups (Abercrombie, Davis, & Shackel, 1963). To the best of our knowledge, this study is the only one that described developmental changes in oculomotor function for children with CP with the limitations of a 50 year old study (measurement accuracy, scoring method, etc.).

In summary, there is a clear lack of quantitative data on the oculomotor performance of a large cohort of children with CP. To fill this gap, we studied eye movements in 51 children with CP, 78 typically developing children and 23 preterm children using an oculomotor task. This task requires an appropriate combination of saccadic and pursuit tracking (de Brouwer et al., 2002). In addition, performance in this task evolves with age during childhood (Ego et al., 2013). Because many children with CP were born preterm, preterm children without CP were also tested in order to dissociate the impact of brain lesion with respect to brain immaturity at birth on oculomotor performance.

Using the oculomotor performance on this large cohort of children with CP, we tried to answer the following questions: (1) Do children with CP suffer from oculomotor deficits and how do these deficits evolve during development? (2) Is there any link between the oculomotor deficit of children with CP and their motor impairment (side of hemiplegia)? (3) Has prematurity an impact on their oculomotor deficit?

2. Materials and methods

2.1. Participants

A cohort of 152 children aged 5–16 years was included in the study. Subjects can be divided in 3 groups: children with a spastic form of cerebral palsy (CP) ($n = 51$), children born preterm with no brain lesion ($n = 23$) and age-matched control children ($n = 78$). In the control group, 58 of the 78 children participated in a previous study (Ego et al., 2013). Children with

Table 1
Characteristics of children with CP.

	n	Age
All CP children	51	11 ± 3 y
Sex		
Boys	29	10.8 ± 3.2 y
Girls	22	10.6 ± 2.9 y
Clinical deficit		
Diplegia	22	10.4 ± 2.8 y
Right hemiplegia	15	12.2 ± 3.6 y
Left hemiplegia	14	9.6 ± 2.2 y
Prematurity		
Preterm	30	10.6 ± 3.1 y
Full-term	19	11.1 ± 2.9 y
Not known (adopted)	2	7.3 ± 0.8 y
GMFCS		
Level I: most independent motor function	33	10.3 ± 2.9 y
Level II	14	12.0 ± 3.5 y
Level III	3	11.0 ± 1.7 y
Level IV	1	9.6 y
Level V: least independent motor function	0	
Vision		
Not available	21	10.9 ± 3.1 y
Available	30	10.5 ± 3.0 y
Normal vision	17	10.6 ± 3.0 y
Strabismus	13	10.8 ± 3.0 y
Nystagmus	3	11.0 ± 1.2 y
Acuity	5	10.1 ± 1.7 y
Visuo-spatial deficit	3	13.7 ± 1.7 y
Other problems	3	12.1 ± 0.6 y
MRI		
Not available	7	9.7 ± 2.5 y
Available	44	10.8 ± 3.1 y
Lesion location		
No lesion	3	8.4 ± 2.5 y
Left	11	10.9 ± 3.9 y
Right	5	8.9 ± 2.1 y
Bilateral	25	11.5 ± 2.8 y
Lesion type		
No lesion	3	8.4 ± 2.5 y
Brain malformation	2	11.3 ± 7.1 y
Abnormality of the periventricular white matter	21	11.2 ± 3.6 y
Cortical/Subcortical lesion	13	10.0 ± 3.7 y
(Sub)cortical lesion and abnormality of the periventricular white matter	5	13.1 ± 3.5 y

GMFCS gross motor function classification system.

CP were selected according to their capacity to sit on a chair and understand the task. Sixty one children with CP were recruited but 4 of them could not participate because they were not able to maintain their trunk and head or were afraid about the task. From the 57 remaining children, 6 were excluded from the analysis because of: problems with data calibration (large nystagmus or an instable fixation $n = 3$), too many blinks and head movements ($n = 2$), too poor eye movements (inability to execute saccades $n = 1$). The characteristics of children with CP whose data are reported are presented in Table 1. Functional severity of cerebral palsy is characterized with the Gross Motor Function Classification System (Palisano et al., 1997). Most of our participating children with CP fall in GMFCS level I and II (mild motor impairment).

After a complete description of the procedure, informed consent was obtained from all parents and participants. All procedures were approved by the Université catholique de Louvain Ethics Committee and were in accordance with the Declaration of Helsinki.

2.2. Experimental set-up and stimuli

Seated on a chair (or their wheelchair if the height was adapted) in a dimly dark room, subjects were asked to look at a target projected by a Barco projector on a screen (195 cm × 145 cm) placed 1.5 m away. Horizontal eye movements of the dominant eye were recorded at 1000 Hz with an infrared eyetracker Eyelink 1000 (SR Research, Ottawa, Ontario, Canada). The dominant eye was determined with a classic eye dominance test using a sheet of paper with a hole. Head movements were restrained using a forehead and chin rest.

Subjects were asked to pursue a 1 deg green dot moving horizontally. Each trial began with an initial fixation on one side of the screen. After the initial fixation period, the target started moving toward the center of the screen at 15 deg/s for 600, 700 or 800 ms after a 3 deg step in the opposite direction (Rashbass, 1961) (1st ramp, Fig. 1A and B). At the end of the

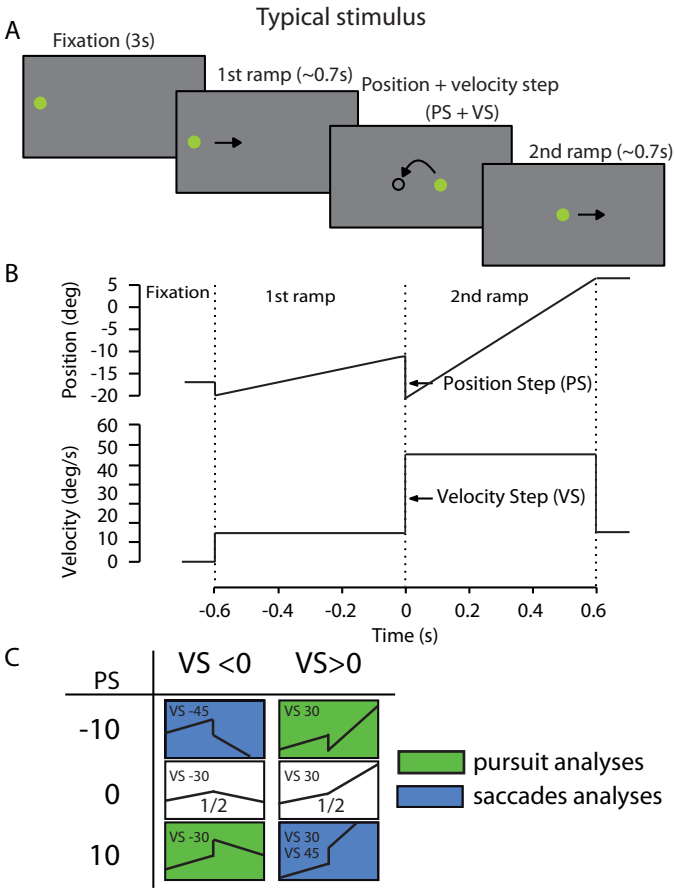

Fig. 1. A: Time course of a trial: After an initial period of fixation, the target started moving at constant velocity for 600, 700 or 800 ms. Then, the target stepped (position step) and continued moving with a different velocity (New velocity = initial velocity + velocity step). B: Typical example of the target position and velocity for a position step (PS) of −10 deg and a velocity step of 30 deg/s. Target velocity on the second ramp is therefore 45 deg/s. C: Boxes represent the different possible combinations of PS and VS. Some conditions (in blue) are used to study saccades. Others (in green) are used to study the pursuit performance. The control condition varied randomly between PS 0 VS 30 and PS 0 VS −30. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

first ramp, the target stepped again and continued moving with a different velocity for 500–800 ms (2nd ramp, Fig. 1A and B). For 58 out of the 78 age-matched controls (first control group), the position step (PS) was randomly chosen between −10, 0 and 10 deg and the velocity step (VS) between ±15, ±30, or ±45 deg/s leading to target velocity for the second ramp ranging between 30 deg/s in one direction to 60 deg/s in the opposite direction. For more details about the experimental procedure, see Ego et al., 2013. This paradigm was slightly adapted for 20 additional controls (second control group), for children with CP and for premature children to maximize the chance of all subjects to perform the task correctly. The initial fixation duration was extended to 3 s and the delay between two consecutive trials was extended to 3 s. Finally, the number of combinations of PS and VS was restricted to 7 as shown in Fig. 1C to reduce the test duration. Only this subset of conditions was analyzed in the present paper.

A typical example of target movement is presented in Fig. 1B. The first control group completed between 10 and 18 blocks of 18 trials corresponding to the 18 different combinations of PS and VS randomly presented. The second (additional) control group, CP and preterm children completed between 10 and 20 blocks of 9–12 trials.

The type of paradigm influenced the pursuit latency but none of the other parameters that were reported in this study. Indeed, the second group had pursuit latency on the first ramp significantly longer than the first group ($F(1,74) = 32.16$, $p = 2 \times 10^{-7}$). For this reason, solely the second control group was taken into account in the analyses of the latency of the pursuit response to the first ramp ($n = 20$). No difference was found in any other pursuit or saccade parameter. The two control groups were merged for all the other analyses ($n = 78$).

2.3. Data analysis

Eye movements were low-pass filtered at 50 Hz with a bidirectional autoregressive zero-phase filter implemented in MATLAB (de Brouwer et al., 2002). Eye velocity and acceleration were obtained from position signals by means of a central

difference algorithm. Saccades were detected using a 500 deg/s^2 acceleration threshold and were removed to obtain the smooth eye velocity traces.

Pursuit performance was analyzed on the first ramp for all trials. Different combinations of PS and VS elicit very different oculomotor responses on the second ramp (see Ego et al., 2013). The conditions with PS and VS with the same sign lead to a high percentage of trials with a saccade just after the position and velocity step. These conditions were used to study the latency and precision of catch-up saccades (blue conditions Fig. 1C). In contrast, the conditions with PS and VS with opposite sign mimic the Rashbass paradigm. The Rashbass paradigm was initially used to reduce the occurrence of saccades during pursuit initiation. Therefore, these conditions were used to study the pursuit performance on the second ramp (green conditions Fig. 1C). Other details of methods are similar to the ones used in Ego et al., 2013. In short, the studied parameters were the onset of the smooth pursuit, the initial eye acceleration and the pursuit gain on the first ramp and on the second ramp (in reaction to the step in position and velocity).

Pursuit onset and acceleration were determined by fitting a piecewise linear function on the smooth eye velocity trace:

$$f(t) = \begin{cases} V & \text{if } t < t_0 \\ V + A(t - t_0) & \text{if } t \geq t_0 \end{cases} \quad (1)$$

where t is the time (s), t_0 is the time of pursuit onset (s), V is the level of eye velocity before pursuit onset (deg/s), and A is the mean acceleration during pursuit initiation (deg/s^2). The constants V, A, and t_0 were the fitted parameters. This function was fitted to the eye velocity on the first 250 ms after stimulus onset to find pursuit onset and acceleration on the first ramp. Pursuit onset and acceleration on the second ramp were computed in 2 steps. First, the time at which the eye velocity deviated from more than two times the standard deviation around the initial velocity at the step gave a first approximation of the onset. Then pursuit onset and acceleration were determined by fitting the same function on an interval starting 100 ms before the step until 150 ms after the previously estimated onset. The gain was defined as the ratio between the mean eye velocity between 450 and 550 ms after first (or second) ramp onset and target velocity.

The mean value of all parameters was computed for each subject and plotted as a function of age. For the analyses on the second ramp, the mean per subject was computed condition by condition. Since the tendencies were the same across conditions, results from the two pursuit conditions were averaged. Similarly, the mean value across the three saccadic conditions was computed. Linear regressions and p-value for the slope were used to assess the evolution of these parameters with age during childhood. Since the number of preterm children was not distributed evenly across age, weighted linear regressions were used for this population. Weights were inversely proportional to the number of children by age.

To assess the asymmetry of the behavior between movements going from left to right and from right to left we computed a coefficient defined as follow:

$$\text{Asymmetry coeff.} = \frac{perf_{\text{to the left}} - perf_{\text{to the right}}}{perf_{\text{to the left}} + perf_{\text{to the right}}} \quad (2)$$

A good oculomotor performance is characterized by short pursuit latency (small onset) and a high pursuit acceleration and gain. To account for these differences, the asymmetry coefficient for pursuit onset was defined as the opposite of the above coefficient. Therefore, positive asymmetry coefficients always represent better performances for leftward movement and negative coefficients represent better performances for rightward movement.

Some trials were excluded from the analyses. The exclusion criteria were different for each computed parameter and were the same as in Ego et al., 2013. Overall, trials with blinks, saccades during pursuit initiation or with position error higher than 5 deg when parameters were computed were removed from the analyses. The percentage of excluded trials ranged from 33% for children with CP for the pursuit gain on the second ramp (vs 15% for control children) to 56% for the pursuit gain on the first ramp (vs 30% for control children). Analyses for children with CP were computed on 5100 trials on average.

3. Results

Oculomotor function improves with age in typically developing children. For instance, when a target starts moving at a constant velocity before suddenly changing trajectory, older children initiate their oculomotor response earlier and faster than younger children (Fig. 2A and B), as reported earlier (Ego et al., 2013). A similar improvement with age is visible in the responses of children with CP to the same moving target (Fig. 2C and D). Most children with cerebral palsy showed eye movements patterns close to control children. They were able to smoothly track the target during the first ramp, to execute accurate saccades in response to the sudden step in position and to keep tracking the moving target using a combination of smooth pursuit and saccades. In addition, while the differences between CP and control children are particularly marked in younger children (Fig. 2A and C), they tend to attenuate in older children. Therefore, by the end of adolescence (14–16 years) pursuit parameters of children with CP were close to those of controls (Fig. 2B and D).

3.1. Children with cerebral palsy have unexpectedly good oculomotor performance

On average, pursuit initiation during the first ramp slightly differed between the two groups (Fig. 3). Indeed the initial pursuit acceleration for children with CP was lower than for control children while pursuit maintenance (between 400 and

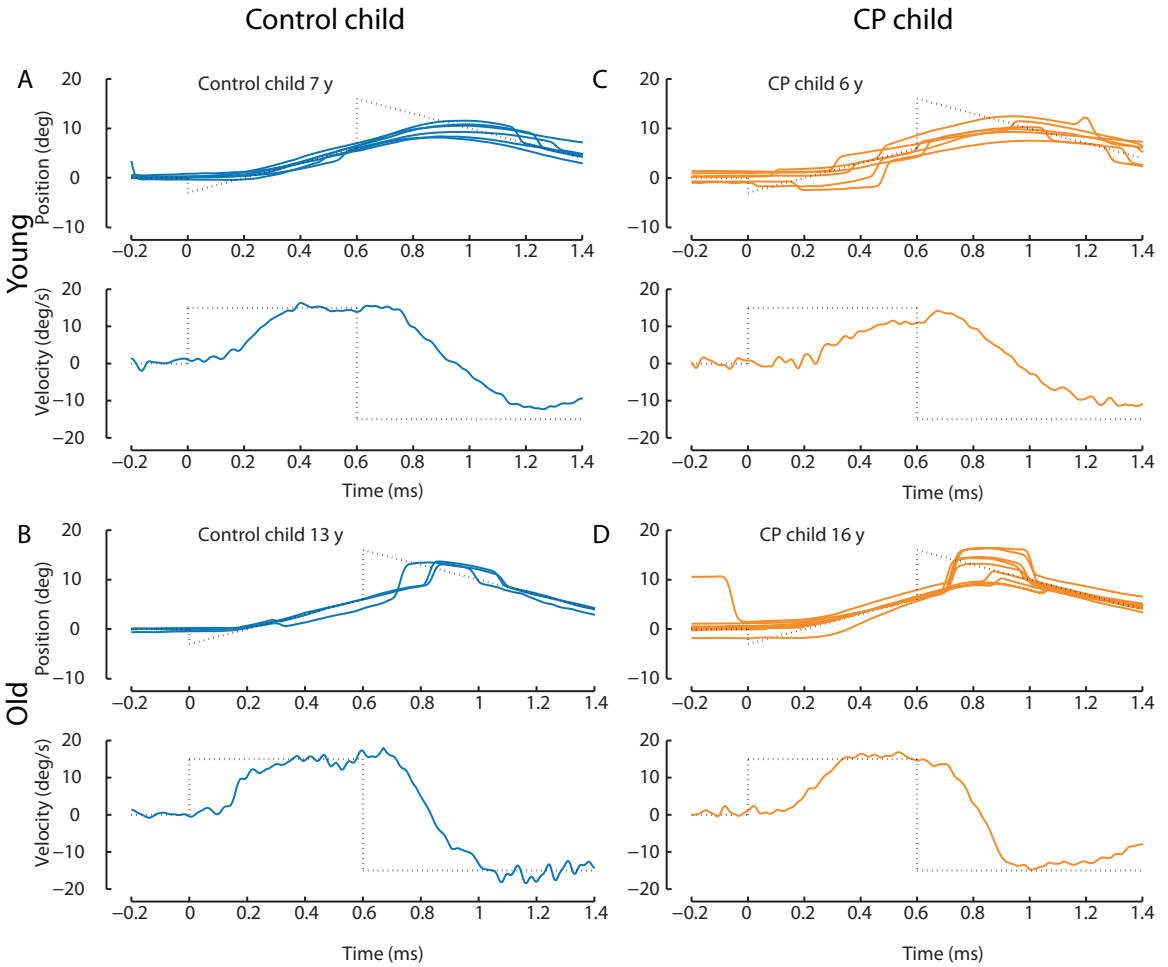

Fig. 2. Typical trials and mean eye velocity of young (top) and older children (bottom). Left panel are trials for control children and right panel for children with cerebral palsy. Dotted lines represent the target motion. These trials are taken from the condition with PS and VS of opposite sign (PS 10 VS-30).

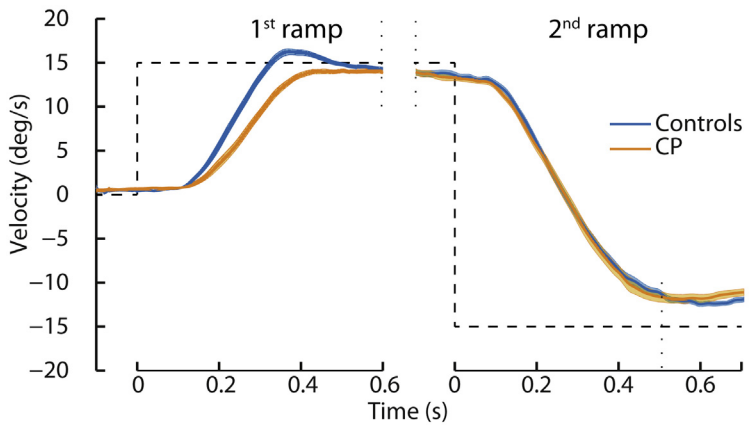

Fig. 3. Mean eye velocity and SEM for all CP ($n = 51$) and the second group of control children on the first ramp and for all control children ($n = 78$) and all children with CP on the second ramp in the case of a position step of 10 deg and a velocity step of −30 deg/s and a target moving initially to the right.

Table 2
Comparison and evolution with age of the smooth pursuit and saccadic performance of control children, preterm children and children with CP.

	% in normal range	CP vs control			Preterm vs CP	Preterm vs control
		F-test Effect size Cohen's *d*	Regression control (Slope and *p*-value)	Regression CP (Slope and *p*-value)		
Onset 1st ramp	67	$F(1,67) = 16.7$, $p = 10^{-4***}$ $d = -1.08$ U3 = 90%	−2.7 ms/y, $p = 0.0015^{**}$	−2.6 ms/y, $p = 10^{-5***}$	$F(1,70) = 6.644$ $p = 0.012^{*}$	$F(1,39) = 1.281$ $p = 0.27$
Acceleration 1st ramp	61	$F(1,125) = 38.4$, $p = 8 \times 10^{-9***}$ $d = 1.06$ U3 = 12.8%	1.85 deg/s^2 y, $p = 6 \times 10^{-5***}$	3.8 deg/s^2 y, $p = 9 \times 10^{-7***}$	$F(1,70) = 8.335$ $p = 0.005^{**}$	$F(1,97) = 5.327$ $p = 0.023^{*}$
Gain 1st ramp	76	$F(1,125) = 4.8$, $p = 0.03^{*}$ $d = 0.38$ U3 = 33.3%	-2×10^{-4}/y, $p = 0.92$	0.01/y, $p = 0.06$	$F(1,70) = 2.398$ $p = 0.13$	$F(1,97) = 0.022$ $p = 0.88$
Onset 2nd ramp	94	$F(1,125) = 3.2$, $p = 0.08$. $d = -0.32$ U3 = 61.6%	−4 ms/y, $p = 4 \times 10^{-5***}$	−5 ms/y, $p = 0.001^{**}$	$F(1,70) = 2.230$ $p = 0.14$	$F(1,97) = 0.036$ $p = 0.85$
Acceleration 2nd ramp	69	$F(1,125) = 14.8$, $p = 2 \times 10^{-4***}$ $d = 0.70$ U3 = 24.3%	3.1 deg/s^2 y, $p = 3 \times 10^{-6***}$	3 deg/s^2 y, $p = 0.002^{**}$	$F(1,70) = 8.625$ $p = 0.004^{**}$	$F(1,97) = 0.210$ $p = 0.65$
Gain 2nd ramp	78	$F(1,125) = 15.7$, $p = 10^{-4***}$ $d = 0.72$ U3 = 29.5%	0.02/y, $p = 8 \times 10^{-4***}$	0.02/y, $p = 0.003^{**}$	$F(1,70) = 6.436$ $p = 0.013^{*}$	$F(1,97) = 0.037$ $p = 0.85$
Latency 1st saccade	92	$F(1,125) = 8.4$, $p = 0.004^{**}$ $d = -0.5$ U3 = 76.9%	−2.7 ms/y, $p = 0.04^{*}$	−8 ms/y, $p = 10^{-5***}$	$F(1,70) = 2.761$ $p = 0.10$	$F(1,97) = 1.39$ $p = 0.24$
Precision 1st saccade	80	$F(1,125) = 3.5$, $p = 0.06$. $d = -0.34$ U3 = 60.3%	−0.08 deg/y, $p = 0.08$.	0.002 deg/y, $p = 0.81$	$F(1,70) = 0.008$ $p = 0.92$	$F(1,97) = 0.890$ $p = 0.35$

* p-value < 0.05.
** p-value < 0.01.
*** p-value < 0.001.

600 ms) was relatively similar. In contrast, during the second ramp, the pursuit response of children with CP was on average very similar to that of control children.

To quantify the overall tracking performance of children with CP during our task, we compared their smooth pursuit parameters to those of age-matched controls. Some of these parameters were related to smooth pursuit initiation during the first and second ramps (smooth pursuit latency and initial acceleration). The quality of the steady state smooth pursuit response was estimated through the average smooth pursuit gain (eye velocity/target velocity). Finally, parameters related to the catch-up saccades elicited in response to the change in target position and velocity were also analyzed (accuracy and latency of the first saccades after the steps).

Most of the studied parameters were significantly different across groups (see Table 2). However, the overlap between the two groups was large as it can be observed for instance on the top panel of Fig. 4A presenting the initial acceleration during the first ramp of the two groups as a function of age for each subject. To assess this overlap, we compared each parameter of each CP subject to the corresponding distribution for the controls, corrected for age. Practically, it corresponds, for each CP subject, to evaluate its performance in comparison to the average performance of age-matched controls, measured by the distance of each orange data point to the blue regression line of controls in Fig. 4A. To this aim, we first built, for each parameter in control children, the histogram of the residuals of the linear regression, representing the spread of this parameter independently of age (blue distributions in Fig. 4B). Then, the regression lines obtained from the control data (blue lines in Fig. 4A) were also taken as a reference for the children with CP in order to obtain a similar distribution. That is, for each CP child, we computed the distance between the value of a parameter and the value from the control regression line (see arrows in Fig. 4A and B). The distribution of this distance was then compared to the distribution obtained in control children (Fig. 4B).

For each parameter, we computed the percentage of children with CP that fell above the 5% percentile of controls (acceleration, gain), below the 95% percentile of control subjects (latency of pursuit or saccades) or within the 2.5–97.5% range (saccade accuracy). These intervals cover the mean values of 95% of the control children. We observed high percentages of children with CP falling within these intervals for the parameters related to either pursuit maintenance or saccades (Fig. 4B, Table 2). For instance, 76% of children with CP had normal pursuit gain during the first ramp and 92% of them had a catch-up saccade latency falling in the control range. The lowest percentages were obtained for parameters related to pursuit initiation for both ramps. During the first and second ramps, only 61% and 69% of the children with CP, respectively, had a pursuit acceleration that fell within the normal range.

3.2. The pursuit performance of children with CP improves with age

One of the hallmarks of this task is the large changes in parameters with age (Ego et al., 2013). For instance, we previously reported age-related increase in pursuit acceleration during the first ramp or decrease in pursuit latency. Similar age-related changes were observed for children with CP (Fig. 4A). Most studied parameters (except pursuit gain on the first ramp and saccadic precision) improved with age (see Table 2).

In children with CP, this evolution of the oculomotor behavior with age could theoretically be either slower than controls, as fast as controls or faster than controls. In the first case, the deficit in target tracking performance would increase with age and would become larger as children get older. In the second case, oculomotor function would undergo similar changes with age across groups. In the last case, the deficit would be larger for younger children but this deficit would decrease with age.

In the data, we found that the oculomotor parameters of children with CP evolved with age at least as fast as the parameters of control children (see Table 2). For some parameters, the improvement with age was even larger in children with CP than in control children. For instance, the initial acceleration during the first ramp increased more with age for children with CP than for control children (see top panel Fig. 4A). That is, while the difference in initial acceleration across the youngest CP and control children was large, this difference was reduced in the oldest children from both groups. This larger change in initial acceleration was associated with a steeper regression slope for children with CP than for control children (Fig. 4A top panel, Homogeneity of slopes test: $F(1,125) = 6.51$, $p = 0.01$). Similarly, the latency of the first saccade after a sudden change in target position decreases faster for children with CP than for control children (Fig. 4A bottom panel, Homogeneity of slopes test: $F(1,125) = 6.48$, $p = 0.01$). The difference in slope did not reach significance for the gain of the first ramp ($F(1,125) = 3.42$, $p = 0.066$).

These differences in evolution with age suggest that impairment of oculomotor performance does not get worst with age. Rather, oculomotor function of children with CP spontaneously improves with age in such a way that deficits in ocumotor tracking are attenuated in older children with CP.

3.3. The pursuit deficit of children with CP is partly linked to their history and motor impairment

(a) Hemiplegic children show moderate asymmetries between rightward and leftward pursuit eye movements

In the previous section, we highlighted that age could account for some of the differences that were observed between the oculomotor behavior of control children and children with CP. Here, we show that clinical features of the children with CP can also account for some of their impairment. That is, the side of hemiplegia is directly linked to the impairment in oculomotor function. The children with CP were categorized into three groups: left hemiplegia, right hemiplegia and others. When the target was moving rightward, left hemiplegic children had poorer tracking performance than control subjects

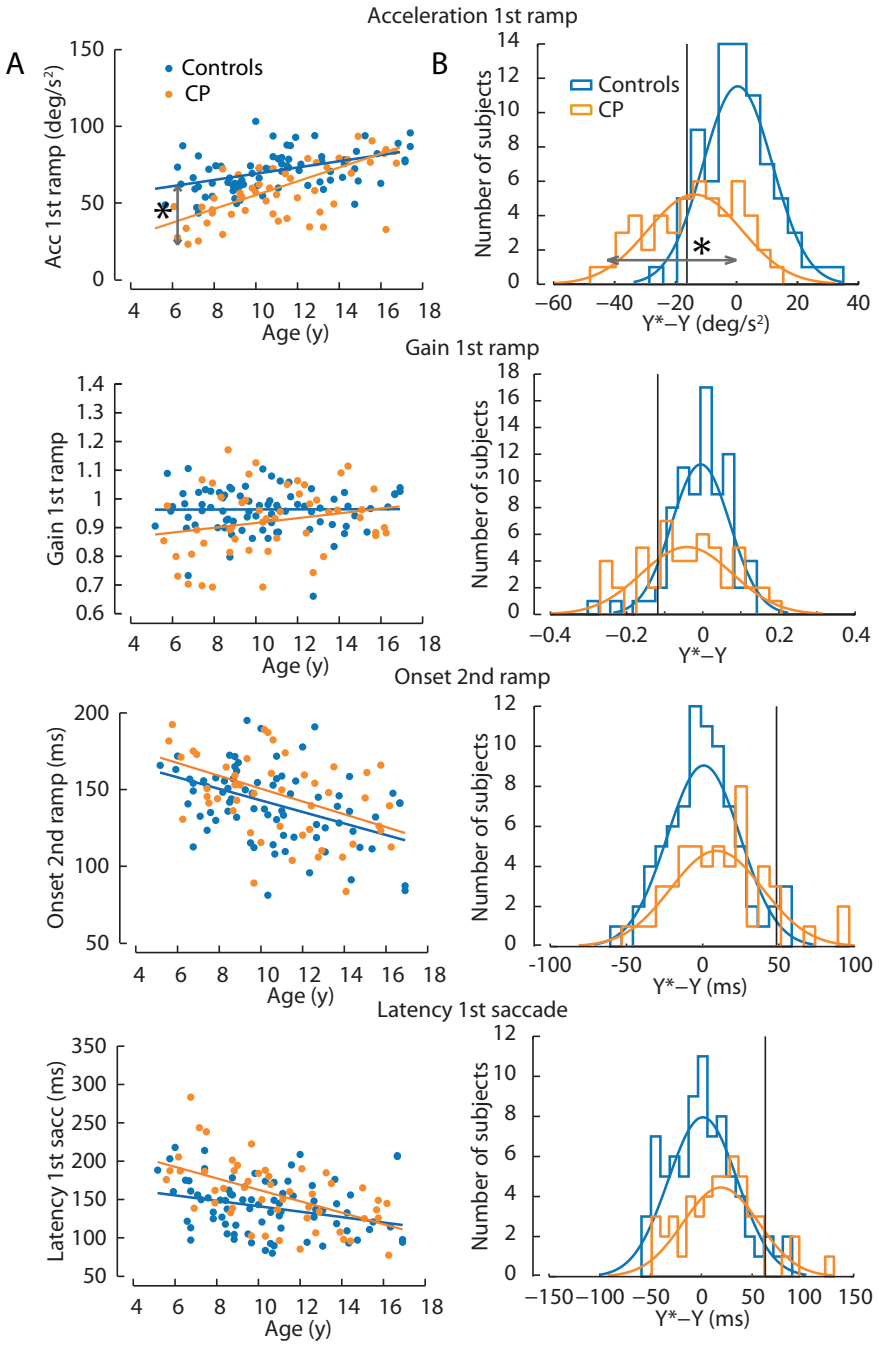

Fig. 4. A: Evolution with age of pursuit acceleration and gain on the first ramp, the onset of the pursuit response on the 2nd ramp and the latency of the first saccade after the position and velocity step. Each dot represents the mean value for one subject. Regression lines for the control children and children with CP are presented. The star represents the difference between the value for one CP subject and the mean value for the controls of his/her age (extracted from the regression line). These differences are used to build the histograms in panel B. B: Histograms of the "normalized" oculomotor performances for the control children ($n = 78$) and children with CP ($n = 51$). Black vertical lines represent the limit of the normal range containing 95% of the control performance. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

or other children with CP (Fig. 5A, right panel). This was also true for right hemiplegic children when the target was moving leftward (Fig. 5A, left panel). This observation was quantified by looking at the asymmetry of the smooth pursuit performance through an asymmetry coefficient (see methods). Positive values of this coefficient are associated with lower performance for rightward target motion while a negative index represents an impairment to leftward target motion. This asymmetry coefficient differed across groups for the three parameters tested (Fig. 5B, main effect of group: Onset: $F(3,124) = 4.95$, $p = 0.003$, Acc: $F(3,124) = 6.351$, $p = 0.0005$, Gain: $F(3,124) = 7.71$, $p = 9 \times 10^{-5}$). Asymmetry coefficients of

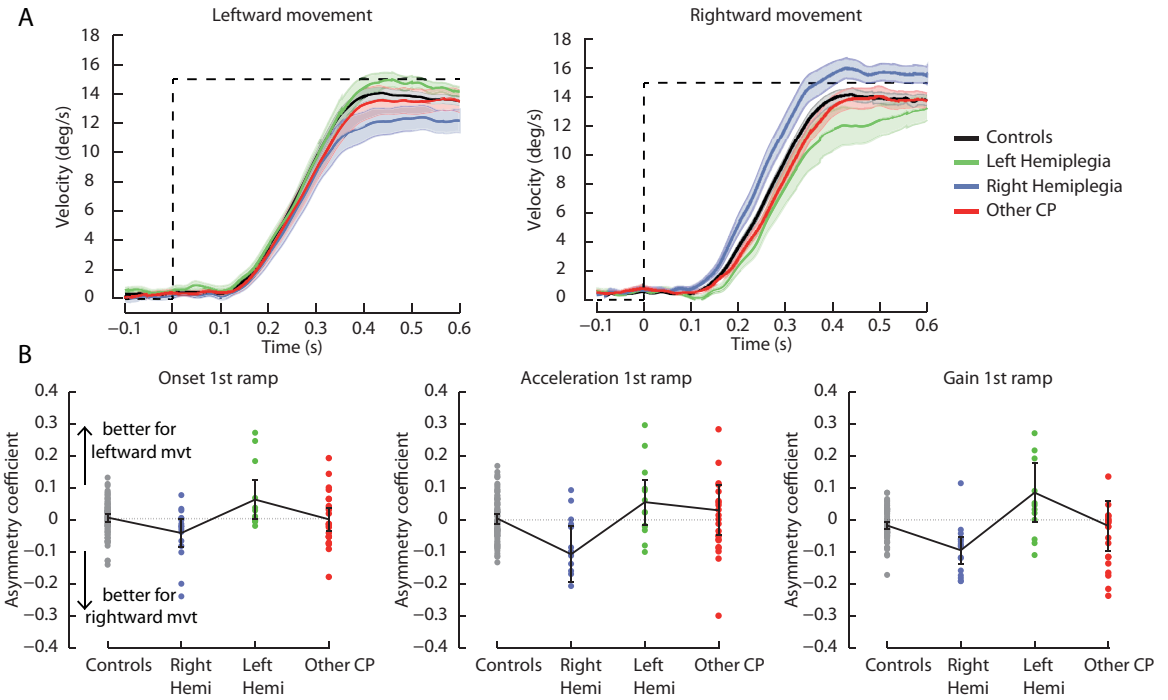

Fig. 5. A: Mean eye velocity profiles on the first ramp for a target going to the right (right Panel) and target going to the left (left Panel). B: Asymmetry coefficient for the onset (left panel), acceleration (middle panel) and smooth pursuit gain (right panel) on the 1st ramp. Positive asymmetry coefficients represent a deficit for rightward movements and negative asymmetry coefficients show an impairment for leftward movements.

right, left hemiplegic children and of the other children with CP were compared to those of control children using Dunnett *t*-tests. Right hemiplegic children had asymmetry coefficients that were more negative than those of control (onset: $p = 0.06$; acceleration: $p = 0.001$; gain: $p = 0.016$). This suggests that these children were impaired for target moving leftward. In contrast, the asymmetry coefficients of left hemiplegic children were higher than those of control children (onset, $p = 0.02$;

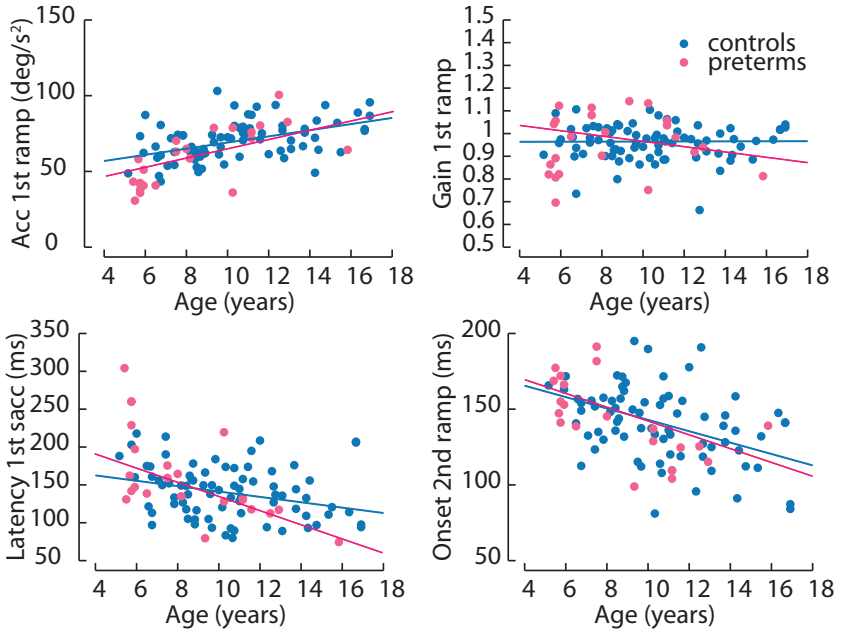

Fig. 6. Comparison of the evolution with age of some pursuit and saccade parameters for controls and preterm children. The pursuit parameters are the pursuit acceleration and gain on the first ramp, the onset of the pursuit response on the 2nd ramp and the latency of the first saccade after the position/velocity step. Each dot represents the mean value for one subject. Regression lines for the control and preterm children are presented.

acceleration $p = 0.36$; gain: $p = 0.003$) meaning that left hemiplegic children exhibited a deficit for rightward movements. None of the asymmetry coefficients of the other non-hemiplegic CP was statistically different from controls (Onset: $p = 0.96$, Acc: $p = 0.81$, Gain: $p = 0.99$).

(b) Prematurity solely cannot explain the oculomotor deficit

Most of the children with CP who participated in this study were born preterm. This raises the question of whether the brain lesion or the prematurity was responsible for the deficit in smooth pursuit performance, which was especially observed in the youngest children with CP. To dissociate the role of brain lesion or brain immaturity on the oculomotor function deficit, we tested 23 preterm children with no brain damage. These preterm children had tracking performances that were very similar to the tracking performance of control children (Fig. 6, Table 2) but significantly different from the performance of children with CP (Table 2). These observations suggest that brain lesion but not brain immaturity impairs oculomotor function.

4. Discussion

The present study gives a quantitative analysis of the visual tracking performance of a large sample of children with cerebral palsy ($n = 51$) with mild motor impairment (mainly GMFCS level I and II). We found that children with CP have an oculomotor function preserved in an unexpectedly large proportion of this population. Moreover, oculomotor function spontaneously improves with age in children with CP, even faster than typically developing children for some of the parameters. The pursuit deficit of these children is partially linked to their clinical disorder. Indeed, hemiplegic children present a deficit for target motion ipsilateral to their lesion. Finally, the oculomotor deficit of children with CP cannot solely be explained by their prematurity.

4.1. The oculomotor function of children with cerebral palsy spontaneously improves with age

One of the main results of the present study is the spontaneous improvement with age of the oculomotor function of children with cerebral palsy. Most abilities of children with CP improve with age. However, children with cerebral palsy and typically developing children have different developmental time course (Kurz, Becker, Heinrichs-Graham, & Wilson, 2014). Some functions of children with CP evolve slower than typically developing children while other functions have a similar or faster developmental time course. For instance, visual perception and IQ do evolve with age but they improve more slowly in children with CP than in typically developing children (Banich, Levine, Kim, & Huttenlocher, 1990; Kozeis et al., 2007; Levine, Kraus, Alexander, Suriyakham, & Huttenlocher, 2005). In contrast, some memory deficits are more pronounced in younger than in older children with cerebral palsy (White & Christ, 2005), which suggests that the evolution of these aspects of memory is faster in children with CP than in typically developing children. Similarly, language development of children with CP also follows this evolution pattern. That is, language deficits of children with CP, which are particularly important in very young children, tend to resolve by school age (Stiles, Reilly, Paul, & Moses, 2005). We report here that the evolution of oculomotor function across childhood was faster than that of control children. This evolution of oculomotor function was spontaneous, as it did not require any therapeutic intervention.

Earlier studies showed improvements of the smooth pursuit and saccadic precision, velocity or reaction time in children with CP after intensive visual motor rehabilitation (Gauthier & Hofferer, 1983; Gauthier, Hofferer, & Martin, 1978). The found spontaneous evolution of oculomotor function suggests that intensive rehabilitation of eye movements by orthoptists may not be necessary for all children with CP. Indeed, we showed that some aspects of the oculomotor function spontaneously recover by participation in daily life activities. For instance, we show that pursuit and saccade latencies or pursuit gain measured on the dominant eye are relatively preserved in a large proportion of the selected children and spontaneously improve with age. However, it does not exclude the need of treatment for some children suffering from large conjugation and version, vergence or accommodation deficits.

In typically developing children, oculomotor function continues to develop lately during childhood and adolescence (Accardo et al., 1995; Ego et al., 2013; Katsanis et al., 1998; Salman, Sharpe, Lillakas, et al., 2006). The present study suggests an even more protracted development of the oculomotor function of children with cerebral palsy. A longitudinal study of their hand function similarly showed improvements over a long time range (between 6 and 21 years) (Eliasson, Forssberg, Hung, & Gordon, 2006). However, in contrast with the spontaneous improvement observed in our study, physical therapy may have a role in this improvement.

The present study shows that early brain damage of CP only leads to limited oculomotor deficit in the children selected for this study. Preserved oculomotor function was also found during a reaching task where gaze patterns were monitored Saavedra, Joshi, Woollacott, & van Donkelaar (2009). Such absence of impairment is likely due to plasticity and brain reorganization after the perinatal brain lesion. Indeed, early brain damage in children with cerebral palsy can be compensated by important and effective reorganization (Eyre, 2007; Krägeloh-Mann, 2004; Staudt, 2010b). In parallel to the reorganization elicited by the brain injury, the brain of any human child undergoes complex changes during development (Kolb, Mychasiuk, Muhammad, & Gibb, 2013), which are driven by neurogenesis, programmed cell death, activity-dependent synaptic plasticity, etc. While it is still unclear whether early brain lesion could alter plastic changes driven by brain development (Kiss, Vasung, & Petrenko, 2014), the brain of children possesses a superior capacity of functional reorganization in comparison with the adult

brain (Staudt, 2010a). In the case of an early brain lesion, injury-related and developmental brain plasticity likely contribute together to the observed improvements with age of the oculomotor function.

4.2. Children with hemiplegia have an asymmetry in their oculomotor function

We found that eye movement deficit was linked to the side of hemiplegia. Left hemiplegic children have a pursuit deficit for rightward target motion and right hemiplegic children have poorer pursuit performance for leftward tracking (Figure 5). In this context, it is very tempting to relate the asymmetry of the pursuit deficit to the laterality of the brain lesion. However, this should be discussed with extreme caution as most of the brain lesions exhibited by our children with CP are not restricted to a single hemisphere. Nevertheless, if we make the reasonable hypothesis that the side of hemiplegia might be the signature of a more profound lack of functionality for the contralateral brain, we can further speculate on the interpretation of our results.

In our protocol, we used a paradigm called step-ramp (Rashbass, 1961). Each trial started with a step in the direction opposite to the future target motion (see Section 2). Therefore, our results first show that children with hemiplegia have a deficit of pursuit initiation for target initially presented in the hemisphere contralateral to the more pronounced functional lesion. This deficit is expressed by increased pursuit latency and decreased initial eye acceleration. At first sight, this observation is in agreement with previous findings on the effect of brain lesion in adults. Indeed, similar pursuit initiation deficits were found in patients with posterior cerebral lesions (Heide, Kurzidim, & Kömpf, 1996; Thurston, Leigh, Crawford, Thompson, & Kennard, 1988) in an identical step-ramp paradigm. This impairment was referred to as a "retinotopic deficit" as step-ramp targets begin to move in the peripheral visual field (Dürsteler & Wurtz, 1988). It is also consistent with the effect of lesion on attention and neglect as cortical or subcortical lesions often impair attentional deficits in the contralesional hemifield (Heide & Kömpf, 1998; Posner, Walker, Friedrich, & Rafal, 1984; Rafal & Posner, 1987). Interestingly, several papers suggest that contralateral neglect is also a common issue of unilateral brain injury (Cermak, 1994; Heilman & Van Den Abell, 1980; Vallar & Perani, 1986) and that such neglect is often associated with right hemisphere lesions, even in children with CP (Heilman & Van Den Abell, 1980; Levine, Warach, Benowitz, & Calvanio, 1986; Moya, Benowitz, Levine, & Finklestein, 1986). These observations suggest that left hemiplegic children should be more impaired in our oculomotor tracking task than right hemiplegic patients. However, we found that both groups of hemiplegic patients exhibited a similar degree of asymmetry in their smooth pursuit response.

The second observed deficit in children with CP is a deficit in pursuit maintenance (lower pursuit gain) for target movement toward the side of the more pronounced brain lesion (ipsi-directional). Such ipsi-directional deficit in pursuit maintenance are commonly found in patients with unilateral lesions in the posterior parietal and temporal lobe junctions, frontal cortex pons or even cerebellar cortex (Baloh, Yee, & Honrubia, 1980; Barton & Sharpe, 1998; Heide et al., 1996; Morrow & Sharpe, 1990, 1993; Sharpe, 2008; Thurston et al., 1988).

The combination of these 2 deficits (retionotopic and ipsi-directional) can be found in absence of visual neglect (Heide et al., 1996; Sharpe, 2008; Thurston et al., 1988) and corresponds to deficits observed after unilateral lesions of the middle temporal (MT) and medial superior temporal (MST) cortex in monkeys (Dürsteler & Wurtz, 1988; Newsome, Wurtz, Dürsteler, & Mikami, 1985). The combination of both deficits may be explained by an impaired ability to estimate the speed of the moving target.

4.3. Brain lesion and not brain immaturity accounts for the oculomotor deficit

In the present study, more than half of the children with CP were born preterm. Altered maturation of cortical circuits is an increasingly recognized aspect of perinatal injury and premature birth (Kiss et al., 2014). Prematurity could therefore explain some of the observed oculomotor deficits. However, we failed to find any significant difference between eye movements of control and preterm children with no brain damage. Similarly, except slightly increased pursuit latency, Newsham et al. found no significant differences in pursuit and saccadic eye movements in children born very prematurely (Newsham, Knox, & Cooke, 2007; Newsham & Knox, 2002). Only the voluntary control of saccadic eye movements is altered. However, Langaas, Mon-Williams, Wann, Pascal, & Thompson (1998) found lower pursuit gain in preterm children than in control children, a finding that we were unable to replicate.

5. Perspectives

First, in this paper we quantified the visual tracking performance of a large group of children with CP and compared it to control subjects as a function of age. We are confident that the differences reported with age are not due to the non-homogeneity of the population with age. Indeed, Table 1 can assess mean age of children is very similar for all GMFCS. Youngest children are not the most affected ones and the evolution cannot be explained by a difference of the impairment with age (see Table 1). Nevertheless, it might be interesting to carry out future studies based on a longitudinal approach and follow the same group of patients from age 6 to age 16 years in order to confirm the results reported in this study.

Second, our study was limited to recording of the dominant eye of subjects. It did not allow studying the eye movement conjugacy which is altered in CP (Lee et al., 1995). Indeed, a large proportion (~50%) of children with CP suffer from strabismus (Barca et al., 2010; Black, 1980, 1982; Fazzi et al., 2012; Kozeis et al., 2007; Palma da Cunha Matta et al., 2008;

Stiers et al., 2002). Our findings do not exclude the presence of gaze disconjugacy but assess the relatively good ocular motility of the dominant eye. Further studies might be based on binocular recordings and simultaneously explore gaze conjugacy in children with CP. However, the large span of strabismic patterns in children with CP would require including a very large number of patients.

Third, individuals with CP showing higher level of GMFCS (most severe) present more pronounced visual deficits since these deficits are rare or absent in children with GMFCS of level I (Ghasia, Brunstrom, Gordon, & Tychsen, 2008). Subjects of this study mostly presented lower level of GMFCS which may partially explain the weakness of the reported deficit. Moreover, because our inclusion criterion for children with CP was based on mild motor impairment, most of our subjects could perform the task quite well. Thus a rather limited number of trials were excluded from the analyses. This proportion was larger in children with CP compared to controls (see methods). However, these percentages are only slightly different and do not alter their ability to perform the task better than expected. Finally, 6 children with CP were excluded from these analyses because they failed performing the task satisfactorily. Theoretically, these subjects may present larger oculomotor deficits. However, our results still represent a large proportion of CP population for which eye movements are only slightly altered. It remains unclear whether it would be feasible to assess oculomotor function quantitatively in children with more severe motor impairment since they might not be capable of performing satisfactorily a visual tracking task.

6. Conclusion

In this study, we used eye movements to provide a window into brain plasticity of children with CP. We showed that oculomotor function spontaneously improves with age in children with CP beyond what was observed during normal development. This improvement indicates that the lesioned brain of children with CP retains the ability to reorganize.

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References

Abercrombie, M., Davis, J., & Shackel, B. (1963). Pilot study of version movements of eyes in cerebral palsied and other children. *Vision Research, 3*(3–4), 135–153.
Accardo, A. P., Pensiero, S., Da Pozzo, S., & Perissutti, P. (1992). Some characteristics of saccadic eye movements in children of primary school age. *Documenta Ophthalmologica. Advances in Ophthalmology, 80*(2), 189–199.
Accardo, A. P., Pensiero, S., Da Pozzo, S., & Perissutti, P. (1995). Characteristics of horizontal smooth pursuit eye movements to sinusoidal stimulation in children of primary school age. *Vision Research, 35*(4), 539–548.
Adelson, E., & Fraiberg, S. (1974). Gross motor development in infants blind from birth. *Child Development, 45*(1), 114–126.
Baloh, R. W., Yee, R. D., & Honrubia, V. (1980). Optokinetic nystagmus and parietal lobe lesions. *Annals of Neurology, 7*(3), 269–276. http://dx.doi.org/10.1002/ana.410070311
Banich, M., Levine, S. C., Kim, H., & Huttenlocher, P. (1990). The effects of developmental factors on IQ in hemiplegic children. *Neuropsychologia, 28*(1), 35–47.
Barca, L., Cappelli, F. R., Di Giulio, P., Staccioli, S., & Castelli, E. (2010). Outpatient assessment of neurovisual functions in children with cerebral Palsy. *Research in Developmental Disabilities, 31*(2), 488–495. http://dx.doi.org/10.1016/j.ridd.2009.10.019
Barton, J. J., & Sharpe, J. A. (1998). Ocular tracking of step-ramp targets by patients with unilateral cerebral lesions. *Brain, 121*(Pt 6), 1165–1183.
Bigelow, A. (1992). Locomotion and search behavior in blind infants. *Infant Behavior and Development, 15*, 179–189.
Black, P. (1980). Ocular defects in children with cerebral palsy. *British Medical Journal, 142*(3), 197–204.
Black, P. (1982). Visual disorders associated with cerebral palsy. *British Journal of Ophthalmology, 66*(1), 46–52.
Blekher, T., Johnson, S. A., Marshall, J., White, K., Hui, S., Weaver, M., et al. (2006). Saccades in presymptomatic and early stages of Huntington disease. *Neurology, 67*, 394–399.
Cermak, S. A. (1994). Assessment of unilateral neglect in individuals with right cerebral vascular accident. *Topics in Geriatric Rehabilitation, 10*(2), 42–55.
Coltellaro, J., LeGare, M., & Terdiman, J. (1995). Eye movements in a small sample of cerebral palsied adults. *Perceptual and Motor Skills, 80*(2), 355.
de Brouwer, S., Yuksel, D., Blohm, G., Missal, M., & Lefèvre, P. (2002). What triggers catch-up saccades during visual tracking? *Journal of Neurophysiology, 87*(3), 1646–1650.
Dürsteler, M. R., & Wurtz, R. H. (1988). Pursuit and optokinetic deficits following chemical lesions of cortical areas MT and MST. *Journal of Neurophysiology, 60*(3), 940–965.
Ego, C., Orban de Xivry, J.-J., Nassogne, M.-C., Yüksel, D., & Lefèvre, P. (2013). The saccadic system does not compensate for the immaturity of the smooth pursuit system during visual tracking in children. *Journal of Neurophysiology, 110*(2), 358–367. http://dx.doi.org/10.1152/jn.00981.2012
Eliasson, A.-C., Forssberg, H., Hung, Y.-C., & Gordon, A. M. (2006). Development of hand function and precision grip control in individuals with cerebral palsy: a 13-year follow-up study. *Pediatrics, 118*(4), e1226–e1236. http://dx.doi.org/10.1542/peds. 2005-2768
Eyre, J. A. (2007). Corticospinal tract development and its plasticity after perinatal injury. *Neuroscience and Biobehavioral Reviews, 31*(8), 1136–1149. http://dx.doi.org/10.1016/j.neubiorev.2007.05.011
Fazzi, E., Signorini, S. G., Bova, S. M., La Piana, R., Ondei, P., Bertone, C., et al. (2007). Spectrum of visual disorders in children with cerebral visual impairment. *Journal of Child Neurology, 22*(3), 294–301. http://dx.doi.org/10.1177/0883073807022003080 1

Fazzi, E., Signorini, S. G., LA Piana, R., Bertone, C., Misefari, W., Galli, J., et al. (2012). Neuro-ophthalmological disorders in cerebral palsy: ophthalmological, oculomotor, and visual aspects. *Developmental Medicine and Child Neurology, 54*(8), 730–736. http://dx.doi.org/10.1111/j. 1469-8749.2012.04324.x
Fukushima, J., Hatta, T., & Fukushima, K. (2000). Development of voluntary control of saccadic eye movements. I. Age-related changes in normal children. *Brain & Development, 22*(3), 173–180.
Gauthier, G., & Hofferer, J.-M. (1983). Visual motor rehabilitation in children with cerebral palsy. *International Rehabilitation Medicine, 5*(3), 118–127.
Gauthier, G. M., Hofferer, J.-M., & Martin, B. (1978). A film projecting system as a diagnostic and training technique for eye movements of cerebral palsied children. *Electroencephalography and Clinical Neurophysiology, 45*(1), 122–127.
Ghasia, F., Brunstrom, J., Gordon, M., & Tychsen, L. (2008). Frequency and severity of visual sensory and motor deficits in children with cerebral palsy: gross motor function classification scale. *Investigative Ophthalmology & Visual Science, 49*(2), 572–580. http://dx.doi.org/10.1167/iovs. 07-0525
Gordon, A. M., & Duff, S. V. (1999). Fingertip forces during object manipulation in children with hemiplegic cerebral palsy. I: anticipatory scaling. *Developmental Medicine and Child Neurology, 41*(3), 166–175.
Heide, W., & Kömpf, D. (1998). Combined deficits of saccades and visuo-spatial orientation after cortical lesions. *Experimental Brain Research, 123*(1–2), 164–171.
Heide, W., Kurzidim, K., & Kömpf, D. (1996). Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain: A Journal of Neurology, 119*(Pt 6), 1951–1969.
Heilman, K. M., & Van Den Abell, T. (1980). Right hemisphere dominance for attention: the mechanism underlying hemispheric asymmetries of inattention (neglect). *Neurology, 30*, 327–330. http://dx.doi.org/10.1212/WNL.30.3.327
Horínek, D., Hoza, D., Cerný, R., Vyhnálek, M., Sturm, D., Bojar, M., et al. (2008). Two cases of improvement of smooth pursuit eye movements after selective posterior rhizotomy. *Child's Nervous System: ChNS: Official Journal of the International Society for Pediatric Neurosurgery, 24*(11), 1283–1288. http://dx.doi.org/10.1007/s00381-008-0673-x
Irving, E. L., Steinbach, M. J., Lillakas, L., Babu, R. J., & Hutchings, N. (2006). Horizontal saccade dynamics across the human life span. *Investigative Ophthalmology & Visual Science, 47*(6), 2478–2484. http://dx.doi.org/10.1167/iovs. 05-1311
Jackson, J., Castleberry, C., Galli, M., & Arnoldi, K. A. (2006). Cerebral palsy for the pediatric eye care team Part II: Diagnosis and treatment of ocular motor deficits. *American Orthoptic Journal, 56*, 86–96. http://dx.doi.org/10.3368/aoj.56.1.86
Katayama, M., & Tamas, L. B. (1987). Saccadic eye-movements of children with cerebral palsy. *Developmental Medicine & Child Neurology, 29*(1), 36–39.
Katsanis, J., Iacono, W. G., & Harris, M. (1998). Development of oculomotor functioning in preadolescence, adolescence, and adulthood. *Psychophysiology, 35*, 64–72.
Kiss, J. Z., Vasung, L., & Petrenko, V. (2014). Process of cortical network formation and impact of early brain damage. *Current Opinion in Neurology*, 133–141. http://dx.doi.org/10.1097/WCO.0000000000000068
Kolb, B., Mychasiuk, R., Muhammad, A., & Gibb, R. (2013). Brain plasticity in the developing brain. *Progress in Brain Research, 207*, 35–64. http://dx.doi.org/10.1016/B978-0-444-63327-9. 00005-9
Kozeis, N., Anogeianaki, A., Mitova, D. T., Anogianakis, G., Mitov, T., & Klisarova, A. (2007). Visual function and visual perception in cerebral palsied children. *Ophthalmic & Physiological Optics: Journal of the British College of Ophthalmic Opticians (Optometrists), 27*(1), 44–53. http://dx.doi.org/10.1111/j. 1475-1313.2006.00413.x
Krägeloh-Mann, I. (2004). Imaging of early brain injury and cortical plasticity. *Experimental Neurology, 190*(Suppl.), S84–S90. http://dx.doi.org/10.1016/j.expneurol.2004.05.037
Krauzlis, R. J. (2004). Recasting the smooth pursuit eye movement system. *Journal of Neurophysiology, 91*(2), 591.
Kurz, M. J., Becker, K. M., Heinrichs-Graham, E., & Wilson, T. W. (2014). Neurophysiological abnormalities in the sensorimotor cortices during the motor planning and movement execution stages of children with cerebral palsy. *Developmental Medicine and Child Neurology*, 1–6. http://dx.doi.org/10.1111/dmcn.12513
Langaas, T., Mon-Williams, M., Wann, J. P., Pascal, E., & Thompson, C. (1998). Eye movements, prematurity and developmental co-ordination disorder. *Vision Research, 38*(12), 1817–1826.
Lee, D. N., & Aronson, E. (1974). Visual proprioceptive control of standing in human infants. *Attention, Perception, & Psychophysics, 15*(3).
Lee, S. K., LeGare, M., & Zhang, H. P. (1995). Conjugate eye movements: comparison of cerebral palsied and normal adults. *Perceptual and Motor Skills, 81*(2), 575.
Leigh, R., & Zee, D. (2006). *The neurology of eye movements.*
Levine, D. N., Warach, J. D., Benowitz, L., & Calvanio, R. (1986). Left spatial neglect: effects of lesion size and premorbid brain atrophy on severity and recovery following right cerebral infarction. *Neurology, 36*(36), 362–366. http://dx.doi.org/10.1212/WNL.36.3.362
Levine, S. C., Kraus, R., Alexander, E., Suriyakham, L. W., & Huttenlocher, P. R. (2005). IQ decline following early unilateral brain injury: a longitudinal study. *Brain and Cognition, 59*(2), 114–123. http://dx.doi.org/10.1016/j.bandc.2005.05.008
Luna, B., Velanova, K., & Geier, C. F. (2008). Development of eye-movement control. *Brain and Cognition, 68*(3), 293–308. http://dx.doi.org/10.1016/j.bandc.2008.08.019
Mayberry, W., & Gilligan, M. B. (1985). Ocular pursuit in mentally retarded, cerebral-palsied, and learning-disabled children. *American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association, 39*(9), 589–595.
Morrow, M. J., & Sharpe, J. A. (1990). Cerebral hemispheric localization of smooth pursuit asymmetry. *Neurology, 40*(2), 284–292.
Morrow, M. J., & Sharpe, J. A. (1993). Smooth pursuit initiation in young and elderly subjects. *Vision Research, 33*(2), 203–210.
Moya, K. L., Benowitz, L. I., Levine, D. N., & Finklestein, S. (1986). Covariant defects in visuospatial abilities and recall of verbal narrative after right hemisphere stroke. *Cortex, 22*(3), 381–397. http://dx.doi.org/10.1016/S0010-9452(86)80003-X
Newsham, D., & Knox, P. C. (2002). Oculomotor control in a group of very low birth weight (VLBW) children. *Progress in Brain Research, 140*, 483–498. http://dx.doi.org/10.1016/S0079-6123(02)40070-2
Newsham, D., Knox, P. C., & Cooke, R. W. I. (2007). Oculomotor control in children who were born very prematurely. *Investigative Ophthalmology & Visual Science, 48*(6), 2595–2601. http://dx.doi.org/10.1167/iovs. 06-1425
Newsome, W. T., Wurtz, R. H., Dürsteler, M. R., & Mikami, A. (1985). Deficits in visual motion processing following ibotenic acid lesions of the middle temporal visual area of the macaque monkey. *Journal of Neuroscience, 5*(3), 825–840.
Orban de Xivry, J.-J., & Lefèvre, P. (2007). Saccades and pursuit: two outcomes of a single sensorimotor process. *Journal of Physiology, 584*(Pt 1), 11–23. http://dx.doi.org/10.1113/jphysiol.2007.139881
Palisano, R. J., Rosenbaum, P. L., Walter, S. D., Russell, D. J., Wood, E., & Galuppi, B. E. (1997). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine & Child Neurology, 39*, 214–223.
Palma da Cunha Matta, A. P., Nunes, G., Rossi, L., Lawisch, V., Dellatolas, G., & Braga, L. (2008). Outpatient evaluation of vision and ocular motricity in 123 children with cerebral palsy. *Developmental Neurorehabilitation, 11*(2), 159–165.
Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience, 4*(7), 1863–1874.
Rafal, R. D., & Posner, M. I. (1987). Deficits in human visual spatial attention following thalamic lesions. *Proceedings of the National Academy of Sciences of the United States of America, 84*(20), 7349–7353.
Ramat, S., Leigh, R. J., Zee, D. S., & Optican, L. M. (2007). What clinical disorders tell us about the neural control of saccadic eye movements. *Brain, 130*(Pt 1), 10–35. http://dx.doi.org/10.1093/brain/awl309
Rashbass, C. (1961). The relationship between saccadic and smooth tracking eye movements. *Journal of Physiology, 159*, 326–338.
Rosen, M. G., & Dickinson, J. C. (1992). The incidence of cerebral palsy. *American Journal of Obstetrics and Gynecology, 167*, 417–423.
Ross, R. G., Radant, A. D., & Hommer, D. W. (1993). A developmental study of smooth pursuit eye movements in normal children from 7 to 15 years of age. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*(4), 783–791. http://dx.doi.org/10.1097/00004583-199307000-00012
Saavedra, S., Joshi, A., Woollacott, M., & van Donkelaar, P. (2009). Eye hand coordination in children with cerebral palsy. *Experimental Brain Research, 192*(2), 155–165. http://dx.doi.org/10.1007/s00221-008-1549-8
Salati, R., Borgatti, R., Giammari, G., & Jacobson, L. (2002). Oculomotor dysfunction in cerebral visual impairment following perinatal hypoxia. *Developmental Medicine and Child Neurology, 44*(8), 542–550.

Salman, M. S., Sharpe, J. A., Eizenman, M., Lillakas, L., Westall, C., To, T., et al. (2006). Saccades in children. *Vision Research, 46*(8–9), 1432–1439. http://dx.doi.org/10.1016/j.visres.2005.06.011

Salman, M. S., Sharpe, J. A., Lillakas, L., Dennis, M., & Steinbach, M. J. (2006). Smooth pursuit eye movements in children. *Experimental Brain Research, 169*(1), 139–143. http://dx.doi.org/10.1007/s00221-005-0292-7

Sharpe, J. (2008). Neurophysiology and neuroanatomy of smooth pursuit: lesion studies. *Brain and Cognition, 68*(3), 241–254. http://dx.doi.org/10.1016/j.bandc.2008.08.015

Staudt, M. (2010a). Brain plasticity following early life brain injury: insights from neuroimaging. *Seminars in Perinatology, 34*(1), 87–92. http://dx.doi.org/10.1053/j.semperi.2009.10.009

Staudt, M. (2010b). Reorganization after pre- and perinatal brain lesions. *Journal of Anatomy, 217*(4), 469–474. http://dx.doi.org/10.1111/j. 1469-7580.2010.01262.x

Stiers, P., Vanderkelen, R., Vanneste, G., Coene, S., De Rammelaere, M., & Vandenbussche, E. (2002). Visual-perceptual impairment in a random sample of children with cerebral palsy. *Developmental Medicine and Child Neurology, 44*(6), 370–382.

Stiles, J., Reilly, J., Paul, B., & Moses, P. (2005). Cognitive development following early brain injury: evidence for neural adaptation. *Trends in Cognitive Sciences, 9*(3), 136–143. http://dx.doi.org/10.1016/j.tics.2005.01.002

Thurston, S. E., Leigh, R. J., Crawford, T., Thompson, A., & Kennard, C. (1988). Two distinct deficits of visual tracking caused by unilateral lesions of cerebral cortex in humans. *Annals of Neurology, 23*(3), 266–273. http://dx.doi.org/10.1002/ana.410230309

Vallar, G., & Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia, 24*, 609–622. http://dx.doi.org/10.1016/0028-3932(86)90001-1

Valvano, J., & Newell, K. M. (2008). Practice of a precision isometric grip-force task by children with spastic cerebral palsy. *Developmental Medicine & Child Neurology, 40*(7), 464–473. http://dx.doi.org/10.1111/j. 1469-8749.1998.tb15397.x

White, D. A., & Christ, S. E. (2005). Executive control of learning and memory in children with bilateral spastic cerebral palsy. *Journal of the International Neuropsychological Society, 11*(7), 920–924.

Yeargin-Allsopp, M., Van Naarden Braun, K., Doernberg, N. S., Benedict, R. E., Kirby, R. S., & Durkin, M. S. (2008). Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. *Pediatrics, 121*(3), 547–554. http://dx.doi.org/10.1542/peds. 2007-1270

Zhang, H. P., LeGare, M., & Lee, S. K. (1998). Effects of three stimulus parameters on eye position in cerebral palsied adults. *Perceptual and Motor Skills, 87*(1), 355.