



Delayed neonatal visual evoked potentials are associated to asymmetric growth pattern in twins



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HIGHLIGHTS

- Twins can represent a valid model to study normal and abnormal neurophysiological development.
- Differences in growth pattern between twins are associated to difference in visual evoked potential (VEP) latency.
- Delayed VEPs may be a neurophysiological marker of relative asymmetric intrauterine growth pattern.

ABSTRACT

Objectives: To study the association between intrauterine growth and visual pathways maturation by neonatal visual evoked potentials (VEPs) in twins, in view of a possible prognostic role.

Methods: Seventy-four twin neonates from 37 pregnancies were selected based on gestational age of more than 30 weeks and uneventful perinatal clinical course. Flash VEPs were recorded at the same post-menstrual age in each twin pair. The association between P2 latency and anthropometric variables at birth was analyzed by comparison within each twin pair and regarding each variable as ordered difference between the two twins.

Results: Analysis of differences within each twin pair highlighted that inter-twin difference in P2 latency was significantly related to difference in ponderal index (PI) ($p = 0.048$).

Expressing the difference in latency as a categorical binary variable, the correlation was significant for both difference in PI, (median difference = -0.36 , 95% CI -0.54 to -0.14 , $p = 0.001$) and difference in body mass index (BMI), (median difference = -1.06 , 95% CI -1.74 to -0.29 , $p = 0.006$).

Conclusions: Lower values of PI and BMI differences are associated to delayed VEP latency in twin pairs. **Significance:** VEP latency suggests reduced myelination of visual pathways when difference in growth pattern occurs in twins.

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Abbreviations: AGA, adequate for gestational age; BMI, body mass index; DCDA, dichorionic diamniotic; DZ, dizygotic; IUGR, intrauterine growth restriction; LED, light emitting diode; MCDA, monochorionic diamniotic; MCMA, monochorionic monoamniotic; MZ, monozygotic; PI, ponderal index; SGA, small for gestational age; VEPs, visual evoked potentials.

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1. Introduction

Gestational age and intrauterine growth are important determinants of central nervous system (CNS) maturation (Padilla et al., 2011). The conventional terminology referring to the failure of intrauterine growth includes two concepts. Firstly, intrauterine growth restriction (IUGR) which describes a foetus which at birth does not reach the estimated target weight for gestational age, thus indicating a progressive reduction in foetal growth during gestation (Unterscheider et al., 2013). The second term is ‘small for gestational age’ (SGA) which refers to a neonate whose weight is

below the 10th percentile for the gestational age, a definition that can underestimate the number of foetuses whose growth trajectories have slowed down, but still do not fall below the 10th percentile threshold at birth (Sanz-Cortés et al., 2010). Prematurity, IUGR, and being SGA, even in the absence of identifiable perinatal neurological impairment, are considered main risk factors for increased neurodevelopmental and cognitive impairment (Dubois et al., 2008; Ballantyne et al., 2016; Shah et al., 2016). Twin research is an informative approach for understanding the genetic and environmental influences affecting human development. In twin pregnancies potential foetal growth impairment is strictly linked to a reduced placental supply of oxygenated blood and nutrients. Twin foetuses show a pattern of growth similar to singletons during the first and second trimester of pregnancy, with a reduction in growth velocity starting usually around 30 weeks of gestation (Atsushi et al., 1999).

A recent study on monozygotic (MZ) and dizygotic (DZ) twins (Yokoyama et al., 2018), demonstrated that shared environmental factors are prevalent over genetic ones. Thus, twin foetuses, in the case of intrauterine growth discordance, provide a natural human model for studying differences in foetal growth and adaptation to progressive *in utero* reduction in nutrients and their effects on the central nervous system (Minghetti et al., 2011), since potential factors which confound the comparison in singletons are reduced in twins. Increased rate of prematurity, intrauterine growth impairment and complications in monochorionic monoamniotic (MCMA) twin pregnancies, explain the higher prevalence of neuro-developmental impairment in twins, compared to singletons (Lorenz, 2012; Babatunde et al., 2018). Birth weight, a crude measure of foetal growth, and gestational age have been reported as better short-term outcome measures, such as Neonatal Intensive Care Unit admission and prolonged hospitalization, than either BMI or PI (Tamim et al., 2004). However, biometric indices, including both weight and length such as Ponderal Index (PI = birth weight/length³) and Body Mass Index (BMI = birth weight/length²) have been widely used by clinicians to better characterize intrauterine growth in relation to symmetry and body composition respectively. Lower values of PI characterize a relative asymmetric pattern of intrauterine growth, occurring in the third trimester and consisting of an initial reduction in the fetal weight growth rate with subsequent slowing of length growth rate (Sharma et al., 2016). The asymmetric growth pattern correlates with delayed myelination (Ramenghi et al., 2011), and suggests a neurodevelopmental risk.

Prognostic indices such as Visual Evoked Potential (VEP) could be useful for early identification of neonates at risk. Visual evoked potentials are electrophysiological signals extracted from electroencephalographic activity in the occipital cortex recorded from the overlying scalp in response to visual stimuli. VEP testing is a non-invasive tool and, among several types of visual stimuli, flashes are less dependent on fixation and more commonly used in young children (Odom et al., 2016). Although VEPs occurring after a flash stimulus are considered to originate in cortical structures, earlier information processing stages in the primary visual pathway are involved during development. In fact, in the neonatal period and until around 48 weeks postmenstrual age, electrophysiological responses cannot be regarded as an index of cortical integrity because they are not cortically mediated (Atkinson, 1984) and VEP latencies correlate to the degree of myelination, synaptogenesis, and neuronal maturation of the primary visual pathways (Dubowitz et al., 1986; Birch and Bosworth, 2004). Remarkable developmental changes in neonatal VEPs have been assessed and several classifications of neonatal VEP waveforms are available in the scientific literature (Tsuneishi et al., 1995; Suppiej, 2007). Flash VEPs can be reliably recorded by light emitting diode goggles (LED Goggles) in preterm newborns as young

as 24 weeks of gestational age, when only a single negative peak at about 300 ms (N300) can be recorded. VEP maturation is then characterized between 32–36 weeks by the appearance of an earlier positive peak, whose latency shows progressive shortening, reaching the near-term value of about 200 ms (P2) (Pike et al., 1999), and coexisting with N300 peak that gradually disappears at around term age, although with an individual variability. The relative stability and lower variability of P2 latency make it a reliable parameter for the evaluation of neonatal brain maturation (Benavente et al., 2005) and for the study of subclinical abnormalities of brain development (Häkkinen et al., 1987; Cainelli et al., 2018). Previous studies on singletons investigating the correlation between intrauterine growth pattern and neonatal VEP maturation showed inconsistent results (Watanabe et al., 1972; Hrbek et al., 1982; Pryds et al., 1989; Petersen et al., 1990; Stanley et al., 1991; Thordstein et al., 2004). Thus, we aimed at investigating the relationship between neonatal VEP latencies and growth parameters in a homogeneous group of twin pairs born from uneventful pregnancies, with normal perinatal clinical course, and tested at the same postmenstrual age. The study of VEPs in twin neonates could offer the unique opportunity of evaluating the effect that different intrauterine growth patterns could exert on cerebral maturation, specifically central visual pathways, without being biased by other clinical and methodological factors. This kind of study has not been previously undertaken and could provide a useful tool for further outcome studies.

2. Methods

2.1. Patients

The study population consisted of 74 twins (57% female), born from 37 pregnancies at the University Hospital in Palermo, Italy. Twenty-eight (76%) of the pregnancies were dichorionic diamniotic (DCDA), 6 (16%) were monochorionic diamniotic (MCDA), and 3 (8%) were monochorionic monoamniotic (MCMA). Sex was concordant in all MCDA and MCMA pregnancies, and in 10 of 28 DCDA pregnancies. Zygosity tests were not available. All newborns included were from Italian parents, inborn and delivered by Caesarean section, eight of which in a state of emergency.

Gestational age was determined from maternal dates of the last menstrual cycle or from the date of embryo transfer for *in vitro* fertilization and confirmed by neurological and clinical examination of neonatal external characteristics. The anthropometric data, gestational and postmenstrual ages of the study population are reported in Table 1.

As reliable neonatal percentile charts for twins were not available for the Italian population, we included in the analysis the results obtained from the adoption of the Italian neonatal anthropometric charts for singletons (Bertino et al., 2010), without adoption of the categorical definition of SGA based on birth weight < 10th percentile (Puccio et al., 2014). Inclusion criteria to be met by both twins were: gestational age \geq 30 weeks, absence of severe perinatal complications, Apgar score \geq 7 at 5 min, normal neonatal cardiovascular adaptation and neurological examination for gestational age at admission. Exclusion criteria were: abnormal neurobehavioural examination for postmenstrual age at discharge, congenital malformations or known abnormal genetic conditions, maternal medical or pregnancy conditions potentially affecting the foetuses, intrauterine exposure to alcohol or drugs with known adverse effect on brain development, full ventilatory support, retinopathy of prematurity more significant than grade 2 and abnormal cranial ultrasounds, including isolated intraventricular haemorrhage superior to grade I and/or periventricular leukomalacia above grade I (de Vries et al., 1992). Supplementary oxygen or

Table 1
Characteristics of the Study Population (n = 74).

	Median	Mean	SD	Range
Gestational Age, wk	35.1	34.7	2.0	30.4–38.4
Birth weight, g	2035	1969	426	980–2800
Length, cm	44	43.4	3.1	34–48
Head circumference, cm	31	30.9	1.6	27.2–35
Postmenstrual age at test, wk	36	35.8	1.4	31.5–38.6
BMI	10.3	10.3	1.4	6.3–13.8
PI	2.34	2.38	0.3	1.58–3.25
P2 latency, ms	214.6	219.1	19.0	186.3–279.3

transitory continuous nasal positive airway pressures were administered in 23 neonates. Biometric parameters, weight, length, head circumference recorded at birth and two biometric indices; Ponderal Index (PI = birth weight/length³) and Body Mass Index (BMI = birth weight/length²), were used for statistical analysis. Ethical approval was granted from the Ethics Committee Palermo 1 of the University Hospital and written informed parental consent was obtained for all patients enrolled in VEP recordings.

2.2. Visual evoked potentials recordings

VEP recordings were performed in both twins on the same day during hospital stay before discharge. The mean postmenstrual age was 35.8 weeks (SD 1.4, range 31.5 – 38.6). Infants were in stable clinical conditions, without phototherapy or respiratory support and VEPs were performed after gavage or bottle feeding in the active sleep state. The active sleep state was defined by observation of the behavioural state characterized by closed eyes, mild body and eye movements, and irregular respiration assessed by visual inspection and concomitant respiratory electronic monitoring and pulse oximetry. The newborns were lying in supine position in the incubator or in a cot with dimmed background. Electrodes were fixed to the scalp with water-soluble paste and tape, the active electrode at Oz, the reference electrode at Fz, and the ground at the right mastoid. The electrode impedance was < 5 kOhm in most recordings but a few were between 5 and 10 kOhm. White light flash stimuli with a duration of 10 ms were delivered using LED goggles presented binocularly at about 5 cm in front of the infant's closed eyes. The stimulation frequency was 0.5 Hz with an intensity of 6 lumen. The recording apparatus was Myoquick (Micromed Ltd., Treviso, Italy). The amplifier bandpass was set at 1–100 Hz. Automatic artefact rejection based on signal amplitude (>±200 µV) was applied. To avoid habituation related to high stimulation rate and high number of stimuli and to ensure reproducibility of the traces, the average consisted of two series of 40 responses, and the stimulus rate was kept at 0.5 Hz (Suppiej, 2007). The analysis time was 1000 ms. All VEP recordings were performed by the same investigator (EP). The analysis was based on identification of the main positive peak (P2) occurring in the time window 100–350 ms from stimulus onset. We chose this specific peak because the relative stability and lower variability of P2 latency make it a reliable parameter for the evaluation of neonatal brain maturation (Benavente et al., 2005). Two investigators (EP, AS), independently evaluated the traces, one of which (AS) was blind to birth, biometric and clinical data. In a few cases a final decision was further agreed on exact P2 latency.

2.3. Statistical analysis

A chi square test for independence was used to compare categorical variables. Non-parametric methods were used for continuous variables in groups (Wilcoxon test, Kruskal Wallis test). Linear regression models were used to compare continuous variables. All

analyses were made considering twins within each pair. This is because twins form part of the same biological system, and are subject to several pregnancy related influences that can affect intrauterine development. Therefore, a dependent analysis can minimize the effects due to pregnancy related issues.

Each pair of twins was ordered considering the twin of higher birth weight as the first twin, and each variable was expressed as the difference between the value in the first twin minus the value in the second twin. We used differences because they are absolute effect measures. Difference in P2 latency was used as outcome variable. Differences in biometric parameters and indices were analyzed in bivariate analyses as possible predictors for difference in P2 latency. Finally, difference in P2 latency was considered as outcome variable in categorized binary form, as positive or negative. Thus, pairs were classified according to the sign of the difference in P2 latency: a positive difference indicates that the twin with higher birthweight has a P2 latency higher than the twin with lower birthweight; a negative difference indicates the opposite. We performed all statistical analyses with the open source statistical software “R”.

3. Results

The differences of the main variables between twin pairs ordered by weight and used to perform the analysis are shown in Table 2.

Results of the analysis performed considering twins in relation to each ordered pair, using the difference in P2 latency as an outcome variable, and differences in biometric parameters (birth weight, length and head circumference) and indices (BMI and PI) as predictors in bivariate analyses, are summarized in Table 3.

No correlation between difference in P2 latency and difference in birth weight, length and head circumference was found in this analysis. Furthermore, no relationship was found between GA and difference in P2 latency (p = 0.231). By contrast, the differences in PI demonstrated a statistically significant inverse relationship with differences in P2 latency (p = 0.048) (Table 3).

In a twin pair, the twin with a lower PI showed on average a longer P2 latency (Fig. 1). Differences in BMI showed a similar, but not statistically significant, inverse pattern. Data were checked for normality using the Lilliefors test, and they appeared to be reasonably normal (p = 0.8313 for differences in latency; p = 0.9268 for differences in PI; p = 0.8596 for differences in BMI). Finally, we repeated the analysis using differences in P2 latency as outcome variables in categorized binary form: positive or negative. The association of a higher birth weight with a longer P2 latency (positive P2 difference) was observed in 23/37 couples (62.16%).

In this analysis we found a statistically significant relationship with both BMI differences (median difference = −1.06, 95% CI −1.74 to −0.29, p = 0.006) (Fig. 2) and PI differences (median difference = −0.36, 95% CI −0.54 to −0.14, p = 0.001) (Fig. 3).

Thus, when in a twin pair the heavier twin showed a longer P2 latency (group with positive P2 differences on the x axis), the value

Table 2
Differences between the values of each variable in each ordered twin pair (n = 37).

Difference in:	Median	Mean	SD	Range
Birth weight, g	180	228	184	10–650
Length, cm	2	1.6	1.8	–3 to 4.5
Head circumference, cm	0.7	0.7	1.1	–1 to 3
Body Mass Index	0.51	0.45	1.1	–1.7 to 3
Ponderal Index	0.05	0.02	0.3	–0.69 to 0.66
P2 latency, ms	5.25	3.78	15.69	–31.25 to 32.81

Table 3
Bivariate analysis of variables expressed as differences in each pair and the difference in P2 latency (n = 37).

Difference in:	R squared	p value
Birth weight, g	0.011	0.538
Length, cm	0.047	0.197
Head circumference, cm	0.017	0.441
Body Mass Index	0.089	0.073
Ponderal Index	0.107	0.048

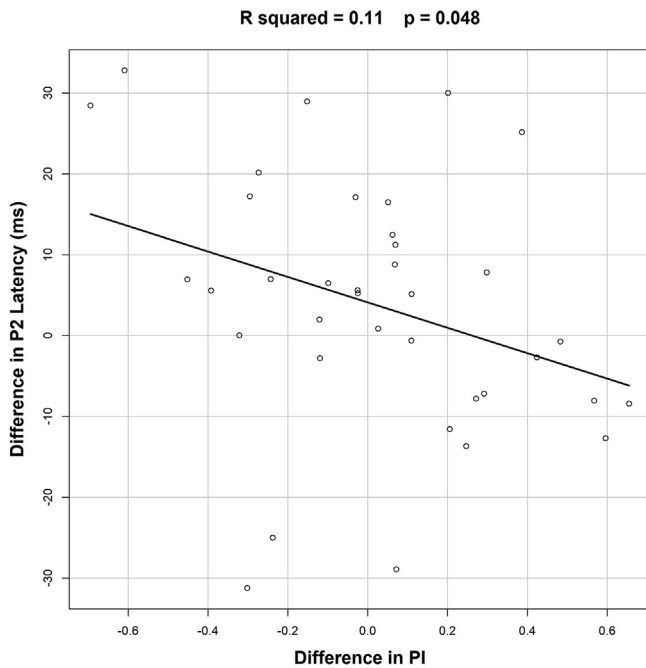


Fig. 1. Scatterplot of difference in Ponderal Index (PI) vs difference in P2 latency in twin couples ordered according to birth weight.

of the differences of BMI and PI tended to be significantly lower, and vice versa. These findings are the expression of the correlation of a lower PI, and less significantly a lower BMI, with differences in VEP latency in the higher birth weight twin.

4. Discussion

This study investigated the relationship between VEP latencies and intrauterine growth parameters in a homogeneous group of twin pairs. We found that a relative asymmetric growth pattern, indicated by a lower PI, was significantly correlated with an increased VEP latency.

Studies investigating the relationship between intrauterine growth impairment and VEP maturation were all performed in singletons and obtained discordant results (Table 4).

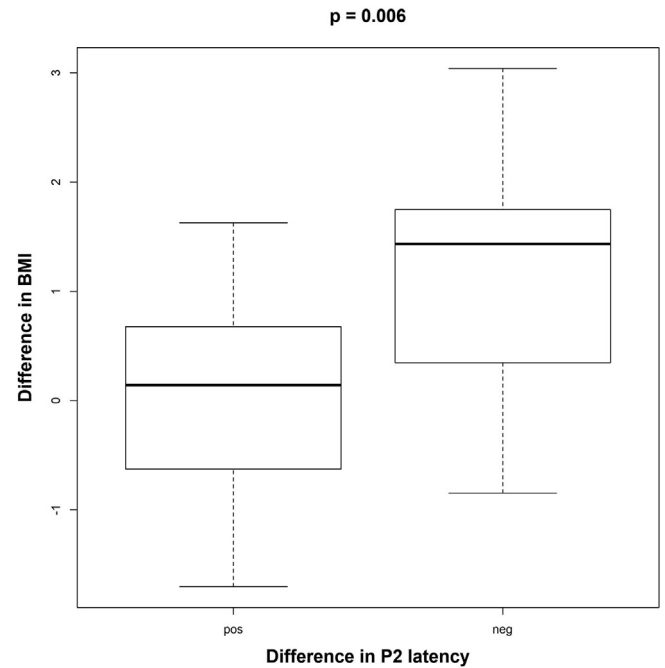


Fig. 2. Box and whiskers plot of the difference in Body Mass Index (BMI) in twin couples ordered by birth weight according to positive or negative difference in P2 latency.

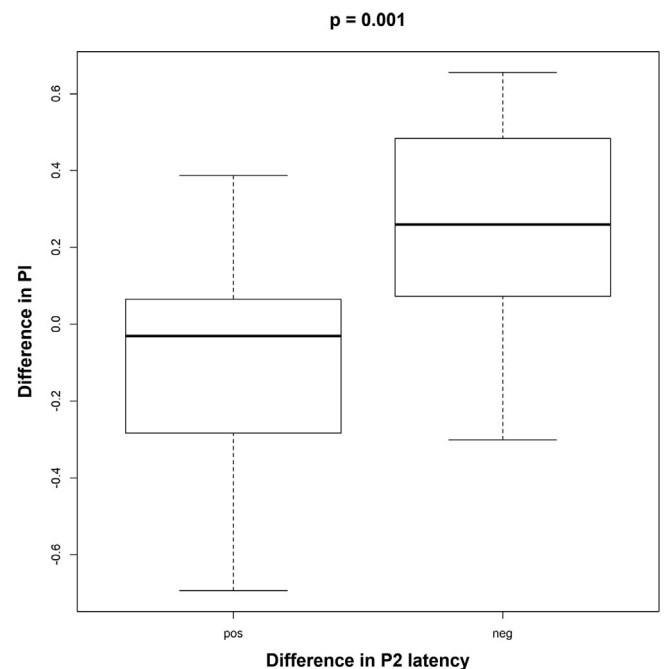


Fig. 3. Box and whiskers plot of difference in Ponderal Index (PI) in twin couples ordered by birth weight according to positive or negative difference in P2 latency.

Table 4
Previous studies on neonatal VEP in IUGR and SGA.

Author	Watanabe K 1972	Hrbeck A 1982	Pryds O 1989	Petersen S 1990	Stanley OH 1991	Thordstein CM 2004	Present study on twins
Sample	AGA/SGA	AGA/SGA	Normal/Asym IUGR	AGA/SGA	Normal/Asym IUGR	Normal/Asym IUGR	Sym/Asym
Total n°	26	62	86	32	64	54	74
GA wks	36–40	37–42	25–34	37–41	32–39	30–42	30–38
Band-pass filters	NA	NA	NA	NA	0.5–100 Hz	0–70 Hz	1–100 Hz
Number of averaged stimuli	20–50	NA	NA	NA	36–64	30–50–50	40
Stimulation rate	0.3–0.5 Hz	0.1–0.3 Hz	Interflash interval of 30 sec	Interflash interval of 30 sec	1 Hz	0.1–0.3–1 Hz	0.5 Hz
Results	Similar VEP wave form and peak latencies	Immature short-wave pattern and increased latency in SGA	No difference in short N1 latency	Shorter P latency in SGA	IUGR negatively affects N2, N3 amplitude and latency	Increased P latency in IUGR	Increased P2 latency is associated to relative asymmetric growth pattern

Abbreviations: IUGR = Intrauterine Growth Restriction, SGA = Small for Gestational Age, AGA = Adequate for Gestational Age, Sym = symmetric growth pattern, Asym = asymmetric growth pattern, NA = not available.

Among previous studies several clinical and methodological issues such as band-pass filter settings, number of averaged stimuli and stimulation rate were different and not always available (Table 4).

Considering clinical issues there is a wide variability in the clinical characteristics of the population studied. Firstly, the enrollment of neonates born at different gestational ages and affected by different perinatal conditions that could affect VEPs maturation can hide the specific effect of impaired growth. The decision to compare growth patterns with VEPs recorded at the same post menstrual age in twin pairs born from uneventful pregnancies and with normal perinatal outcome allowed us to evaluate the effect of growth only, without other confounding factors and to reduce potential biases. In fact, VEPs were performed using the same methodology at the same post menstrual age in both twins for each pair. Moreover, neither neurological evaluation nor US brain imaging were pathological at the moment of hospital discharge. One other strength of the present study was the choice of supplementary growth parameters. Previous studies evaluated VEP latencies in relation to conditions such IUGR and SGA, terms often used interchangeably and with different cut-off values. We hypothesized that PI and BMI, widely used by clinicians in several settings because they include both weight and length, could better evaluate the effect of the intrauterine body disproportion and nutritional status in a low risk group of subjects. It is known that BMI has a steady increase up to 38 weeks of gestation, then a leveling off up to the 40th week and a slight decrease up to the 42th week in both sexes (Brock et al., 2008). BMI is higher among males (Guihard-Costa et al., 1997), but fits better in case of stratification for gestational age (Ferguson et al., 2018). PI shows no sex difference (Guihard-Costa et al., 1997), is uncorrelated with length up to 39 weeks of gestation (Cole et al., 1997), it is the preferable biometric index regardless of the considered gestational age (Ferguson et al., 2018), and has been more frequently used for the distinction between symmetric and asymmetric IUGR patterns (Landmann et al., 2006). In studies on neonates with IUGR a trend towards lower cortical and white matter volumes correlated to neurobehavioural scores at term has been described (Dubois et al., 2008) and the asymmetric pattern has been linked to more health problems than those occurring in symmetrically grown neonates (Dashe et al., 2000). We used PI without applying, as was done in previous studies (Puccio et al., 2013), an arbitrary cut-off value for PI. Instead, we evaluated the relative symmetric vs asymmetric growth patterns based on differences in PI as a continuum. We found that the best correlation with VEP latency was obtained

using the relative asymmetric growth pattern defined by the differences in PI. A lower PI in the relatively asymmetric twin of the pair was associated with prolonged latency. This finding is relevant since it might represent a delayed myelination in agreement with MRI studies in IUGR preterm infants at term-equivalent age (Ramenghi et al., 2011). Furthermore, research showed that white matter involvement in the critical phase of neuronal migration may interfere with cortical development, representing a risk for children's future intellectual performance (Poduri and Volpe, 2018). Unfortunately, the lack of follow up data, not yet completed in our population, does not allow to evaluate whether differences in VEP latencies between co-twins (with longer VEP latencies in the co-twin with lower PI) represent a delay in maturation of the visual pathways or a marker of future developmental disorders. Indeed, in other population settings, such as hypoxic ischemic encephalopathy, absent neonatal VEPs predicted visual impairment in severely asphyxiated neonates developing cerebral palsy (Suppiej et al., 2010). Moreover, in moderate neonatal hypoxic ischemic encephalopathy managed with hypothermia without clinical or MRI abnormalities in the neonatal period, less severe VEPs abnormalities were associated to low scores on the Griffiths developmental scales at two years of age (Cainelli et al., 2018). VEPs elicited by luminance variations such as white light flashes widely activate multiple interconnected brain areas so, it is plausible that they do not reflect only visual impairment. Indeed, in one other study visual impairment at follow up was seen only in those with absent responses (Suppiej et al., 2010).

VEPs may prove to be a useful prognostic tool with the advantage of being performed in the standard clinical setting as in incubator or in a cot.

Weaknesses of the present study are the wide range of post menstrual age at VEP testing and the preclusion of obtaining results in terms of MZ or DZ status, owing to the non-availability of zygosity tests for 20 sex concordant twins from 10 DCDA pregnancies

In conclusion, using specific anthropometric measures, we were able to demonstrate a correlation between intrauterine growth pattern and VEP latency. This consisted in delayed latency in the twin with a lower PI (marker of relative asymmetric growth), in comparison to the co-twin. Notably these findings occurred in the absence of other identifiable risk factors at birth and at hospital discharge, and may represent a signature of reduced myelination of the visual pathways. We therefore suggest that PI and VEPs should be included in the evaluation of the evolutionary risk profile of twins, in view of individualized follow-up programs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Further reading

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