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Long-term impact of prenatal exposure to chemotherapy on executive functioning: An ERP study

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HIGHLIGHTS

- Prenatal chemotherapy exposure was found to affect response inhibition and spatial attention.
- Prenatal chemotherapy exposure and prematurity might alter the development of conflict monitoring.
- All pros and cons of late-premature induction over treatment during pregnancy should be considered.

ABSTRACT

Objective: This study examines the long-term impact of prenatal exposure to chemotherapy on executive functioning and the contribution of late-prematurity to this effect, using event-related potentials.
Methods: Mothers of the prenatal-exposed children (n = 20) were diagnosed with cancer and received chemotherapeutic treatment during pregnancy. We recruited healthy controls (n = 20) who were matched on a 1:1 ratio regarding prematurity, age and sex.

We assessed executive functioning at the age of nine, using two event-related potential paradigms: a Go/Nogo paradigm to investigate processes of response inhibition and conflict monitoring, as well as a Posner paradigm to investigate spatial attention.
Results: Lower potentials were found in prenatal-exposed children compared to controls in the Go/Nogo P3 and Posner positive slow wave. Moreover, prenatal-exposed children responded slower on the Posner paradigm compared to controls ($p < .033$), with more incorrect responses ($p = .023$). In the control group, the N2 Go/Nogo wave was more pronounced in children born after a longer gestation.
Conclusions: This is the first study that demonstrates an effect of prenatal exposure to chemotherapy on the development of executive functioning, not limited to the effect of late-prematurity.
Significance: This study emphasizes the necessity of a long-term follow-up of prenatal-exposed children to re-inform clinical practice on the costs and benefits of late-premature induction over treatment during pregnancy.

Abbreviations: CCA, Canonical Correlation Analysis; ERP, Event-related potentials; GA, Gestational age; INCIP, International Network on Cancer, Infertility, and Pregnancy; PSW, Positive slow wave; RM-ANOVA, Repeated measures analysis of variance; SGA, Small for gestational age; WISC, Wechsler Intelligence Scale for Children.

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1. Introduction

About one in thousand pregnancies are complicated by cancer (de Haan et al., 2018). Multiple studies (Van Calsteren et al., 2010a, 2010b, 2010c; Amant et al., 2012, 2015b; Cardonick et al., 2015; de Haan et al., 2018) indicated that chemotherapy can be safely administered after the first trimester of pregnancy (Amant et al., 2015a) without major sequelae for the offspring. However, these studies do show a high occurrence of (late-)prematurity (48%), as well as a high rate of children being born small for gestational age (SGA, 21% born below 10th birthweight percentile) (Amant et al., 2015b; Cardonick et al., 2015; de Haan et al., 2018). Unfortunately, these studies had a limited follow-up period (≤3y) (Amant et al., 2015b) or observed populations with heterogeneous ages (Amant et al., 2012; Cardonick et al., 2015). As a result, the effects of in utero exposure to cancer therapy on development past the age of three remain largely unknown, stating the need for a longer follow-up.

Chemotherapy-induced neurotoxicity has been documented in pediatric (Sleurs et al., 2016, 2018) and adult (McDonald et al., 2013; Janelsins et al., 2014; Ahles and Root, 2018) cancer populations. Though most chemotherapeutic agents only partially cross the placental barrier (Berveiller et al., 2016), cancer and chemotherapy in utero could also affect neurodevelopment through indirect pathways, such as maternal nutrition (Veena et al., 2016), inflammation (Richetto and Riva, 2014), stress (Richetto and Riva, 2014; Bock et al., 2015) and anxiety (Mennes et al., 2006, 2009), as well as other factors (Vercruysse et al., 2016). This further emphasizes the need for a long-term cognitive follow-up of children who are prenatally exposed to cancer therapy.

Literature on the direct cognitive impact of chemotherapy shows executive functioning to be especially vulnerable (McDonald et al., 2013; Deprez et al., 2014; Janelsins et al., 2014; Sleurs et al., 2016). Executive functioning develops from early childhood, through adolescence and into adulthood (Karbach and Unger, 2014). As previous studies investigating in utero exposure to cancer therapy did not systematically include older children (Amant et al., 2012, 2015b; Cardonick et al., 2015), longer-term effects on executive functioning have not yet been assessed.

By comparing event-related potentials (ERP) in prenatal-exposed children at the age of nine with a matched control group, the current study attempts to examine possible long-term neurocognitive impact of prenatal exposure to chemotherapy on executive functioning, and the contribution of late-prematurity to this effect.

2. Methods

2.1. Participants

This study is based on the Belgian cohort of the international follow-up study by the International Network on Cancer, Infertility, and Pregnancy (INCIP). Mothers of prenatal-exposed children (n = 20) were diagnosed with cancer and received chemotherapeutic treatment during pregnancy (with or without surgery), but no radiotherapy. Children in the control group, born to healthy mothers, were matched on a 1:1 ratio regarding gestational age (GA), age and sex, in accordance with the methodology applied by Amant et al. (2015b). Exclusion criteria were major obstetrical and neonatal complications which possibly affect cognitive development (e.g. neonatal infections, pre-eclampsia, …). All children were tested between 2010 and 2018 at the age of nine years. Full scale IQ was assessed using the Wechsler Intelligence Scale for Children (WISC, version III or V) (Wechsler, 1991, 2014). The study was approved by the local ethical committee and conducted in accordance with the Declaration of Helsinki. The prenatal-exposed group overlaps partially the samples included in previous studies by Amant et al. (2012, 2015b) though only 1 child was previously included at the age of nine.

2.2. Paradigms

During task execution, participants were comfortably seated in front of a 19-inch screen at an approximate distance of 1 m.

First, using a Go/Nogo paradigm, we investigated processes of response inhibition, as reflected in the central to parietal P3 wave, and conflict monitoring, as reflected in the frontal N2 wave (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004; Harper et al., 2014). Participants were instructed to press a button when a square (Go) appeared in the middle of the screen and suppress response when a circle (Nogo) appeared instead (both stimuli: visual angle = 1.1°, duration 1.5 s). Inter-stimulus time was randomly jittered between 2.5–3 s. When there was no stimulus presented, the participants were presented with a fixation cross in the middle of the screen. All participants completed one run, containing 120 trials of which 80% were Go-trials.

Second, using the Posner paradigm (Posner, 1980), we investigated reorienting of attention. Earlier, more lateral, P1 and N1 ERP components in this paradigm reflect visual task detection, whereas the later parietal to occipital P3 wave and positive slow wave (pSW) reflect response selection and attentional set updating (Perchet and Garcia-Larrea, 2000; Slagter et al., 2005). Children were presented during the whole paradigm with an empty box (visual angle = 2.9°) on the left and right side of the screen, with a fixation cross in the middle (4° off-center). During the task a geometric figure (square, triangle or circle, visual angle = 1.1°, duration = 600 ms) appeared equiprobably within one of both boxes. Children were given a button in each hand and were asked to respond with the button according to which side the figure appeared. Some trials were preceded by either an endogenous (an arrow in the middle of the screen pointing left or right, visual angle = 1.1°, duration = 300 ms) or exogenous (one of both boxes doubling in thickness, duration = 300 ms) cue, which was valid (i.e. the cue directed attention to the side of the screen on which the task stimulus later appeared) in 75% of the cases. Between each cue and task there was an equiprobable time interval of either 400 or 550 ms. After each task there was a randomly jittered time interval between 2–3 s before the next cue or task appeared. Each participant completed 3 runs, each consisting of 110 trials of which 30 were not cued, 40 were preceded by an endogenous cue and 40 were preceded by an exogenous cue. Before the first run, the children completed a short practice run to ensure understanding of the task.

2.3. EEG recording and analysis

EEG signals were acquired with 31 Ag/AgCl ring electrodes (Easy Cap) placed according to the international 10–10 system at following locations: Fp1, Fp2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, FT9, FT10, Cz, C3, C4, T3, T4, CP1, CP2, CP5, CP6, Pz, P3, P4, T5, T6, O1, O2, PO9, PO10. Two linked mastoid electrodes were used as a reference. Horizontal and vertical EOG was both acquired with two electrodes, respectively at the outer canthi of the eyes and above/below the left eye. A sampling frequency of 1000 Hz was used with an online 12 bits A/D conversion and 70 Hz low-pass filtering (Schwarzer Ahms 40 channels headbox). The impedance of all electrodes was set below 20 kΩ.

All EEG processing was performed using a combination of EEGLAB (v14.1.1) and in-house MATLAB (v2017b) scripts. All data were band-pass filtered with a bandwidth of 0.5–40 Hz and resampled to 500 Hz. Automated artifact rejection based on independent component analysis (extended-ICA) was performed with the EEGLAB MARA plugin (v1.2) (Winkler et al., 2011, 2014).

Subsequently, EMG artifacts were automatically removed using Canonical Correlation Analysis (CCA) (De Clercq et al., 2006). Bad channels were identified having a kurtosis over 5SD over a whole run compared to the other channels, and spherically interpolated (Urigüen and Garcia-Zapirain, 2015). Afterwards all data was epoched with regard to the onset of the task stimulus. The epoch interval was from −200 to 1000 ms for Go/Nogo trials and from −750 to 1000 ms for Posner trials. Only correct trials (correct response within 150 to 2000 ms) were considered for further analysis. The baseline interval was from −200 to 0 ms for Go/Nogo trials and −750 to −550 ms for Posner trials. The baseline average was subtracted from each epoch. Trials having a joint probability or kurtosis higher than 4 SD compared to other trials were rejected (Urigüen and Garcia-Zapirain, 2015). ERP's were constructed for each subject by averaging epochs separately for each stimulus type for Go/Nogo trials and for each combination of cue type (Endogenous, Exogenous or no cue) and cue validity (valid or invalid) for Posner trials. To increase SNR and decrease multiple testing, ERPs were averaged along electrode clusters (Trujillo et al., 2009; Harper et al., 2014). For the Go/Nogo paradigm frontal (F3, Fz, F4), central (C3, Cz, C4) and parietal (P3, Pz, P4) regions were selected and for the Posner paradigm parietal (P3, Pz, P4) and occipital (O1, O2) regions were selected.

To visualize group differences, group average ERPs were created for each condition of each paradigm. Similarly, to visualize effects of GA within both groups, average ERPs were created for preterm (GA < 37 weeks, n = 11 in both groups) and term (GA ≥ 37 weeks, n = 9 in both groups) children in both groups separately.

2.4. Statistical analysis

Demographic data were compared between both groups (SPSS v25), using Mann-Whitney U-test for ordinal and numerical data, and Fisher's exact test for nominal data. Median response times during correct trials for each subject and trial type, as well as rates of false alarms, misses and incorrect responses were compared between prenatal-exposed and control children using Mann-Whitney U-test.

Group effects were assessed for each ERP time point of each ERP cluster, using repeated measures ANOVA (RM-ANOVA) with group and GA (defined in days) as between-subject variables. For the Posner paradigm these analyses were performed for each cue type separately. The within-subject variables for the Go/Nogo and Posner paradigms were condition (Go vs. Nogo) and cue validity (valid vs. invalid), respectively. Similarly, effects of GA were assessed for each group separately using RM-ANOVA with GA as a continuous between-subject variable. Significance was inferred at a threshold of $p < .05$ corrected for nonsphericity using Greenhouse-Geisser correction, and Bonferroni corrected for number of tested electrode clusters (i.e. 3 and 2 for Go/Nogo and Posner respectively) over a minimal consecutive time interval of 10 ms (5 samples) (Schrooten et al., 2017).

Table 1
Population characteristics. Continuous parameters are reported with median and range per group, whereas frequencies are reported with the absolute count as well as the percentage. Ordinal and numeric parameters were compared between both groups using Mann-Whitney U-test and categorical parameters using Fisher's exact test (underlined). Significant results (*p < .05, uncorrected*) are indicated in bold. Min: minimum. Max: maximum.

	Prenatal-exposed group			Control group			Statistics
	Median	Min	Max	Median	Min	Max	P-value
Age (years)	9.18	8.79	9.94	9.58	9.07	9.97	***0.001***
GA (weeks + days)	35 + 6	28 + 3	40 + 1	36 + 0	28 + 2	40 + 0	*0.799*
Birth weight (g)	2903	1405	3905	2793	940	3410	*0.565*
Maternal age at birth (years)	34	25	40	30	26	39	***0.009***
Total IQ	106	74	130	109	62	128	*0.149*

	Count	Percentage	Count	Percentage	P-value
N	20		20		
Twins	2		2	10%	*1*
Corrected vision	8	40%	6	30%	*0.523*
Sex					*1*
Male	9	45%	9	45%	
Female	11	55%	11	55%	
Ethnicity					*0.113*
Caucasian	17	85%	17	85%	
Asian	1	5%	0	0%	
African	2	10%	0	0%	
Mixed	0	0%	3	15%	
Handedness					*0.695*
Right	15	75%	17	85%	
Left	5	25%	3	15%	
Level of education parents					
Mother					*0.583*
Primary school	1	5%	0	0%	
Secondary school	8	40%	3	15%	
Bachelor	3	15%	12	60%	
Master	8	40%	5	25%	
Father					*0.355*
Primary school	1	5%	0	0%	
Secondary school	9	45%	5	25%	
Bachelor	3	15%	8	40%	
Master	7	35%	7	35%	
Smoking or drugs during pregnancy	0	0%	0	0%	*1*
Alcohol during pregnancy					*1*
Yes	2	10%	1	5%	
Unknown	1	5%	1	5%	

2.5. Data availability statement

The anonymized data that support the findings of this study, as well as related documents, are available from the corresponding author upon reasonable request.

3. Results

3.1. Demographic and medical data

Population characteristics are shown in Table 1. IQ data were missing for two children of the prenatal-exposed group. A Mann-Whitney U-test indicated a slightly younger age at testing in prenatal-exposed children (median = 9.18 years) compared to the control group (median = 9.58 years), $p = .001$. However, the age range of both groups was similar and narrow (8.79–9.97 y), reducing possible effects of aging. Maternal age was higher in the prenatal-exposed group (median = 34 years) compared to the control group (median = 30 years), $p = .009$. This can partially be explained by the higher incidence of cancer with age (Arnold et al., 2015). Additional information on cancer types and chemotherapy regimens administered during pregnancy is available in Table 2.

3.2. Behavioral performance

Response times and correctness are summarized in Table 3. For the Go/Nogo paradigm we observed no significant between-group differences on any response measure. However, in the Posner paradigm, median response times were delayed in the prenatal-exposed group for all cued conditions ($p < .033$) and this group also had more incorrect responses (Median 0.9% compared to 0.3% in the control group, $p = .023$). However, the number of incorrect responses and misses remained relatively low in both paradigms (<2.6%) with only a slightly elevated false alarm rate in the Go/Nogo paradigm (median of 10.4% and 12.5% respectively for the prenatal-exposed and control group).

3.3. ERP results

The amount of data, per subject and condition, that was excluded due to artifacts, remained low in Posner (median $\leq$ 1.11%,

Table 2
Maternal tumor types and treatment during pregnancy. Chemotherapy regimen and number of cycles are mentioned as administered during pregnancy. FEC: 5-fluorouracil, epirubicin and cyclophosphamide. FAC: 5-fluorouracil, doxorubicin (adiamycin) and cyclophosphhamide. AC: doxorubicin and cyclophosphamide. ABVD: doxorubicin, Bleomycin, Vinblastine, Dacarbazine. Ara-C: cytarabine. R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone. Min: minimum. Max: maximum.

Maternal disease	**Count**	**%**			
Breast cancer	12	60%			
Cervical cancer	2 (twin)	10%			
Hodgkin lymphoma	2	10%			
Non-Hodgkin lymphoma	1	5%			
Acute lymphoblastic leukemia	1	5%			
Acute myeloid leukemia	1	5%			
Colon carcinoma	1	5%			
Chemotherapy during pregnancy			**Cycles**		
			Median	Min	Max
FEC/FAC	7	35%	6	2	6
AC	3	15%	4	3	5
ABVD	2	10%	3	2	4
Neo-adjuvant platinum	2 (twin)	10%	3		
5-fluorouracil	1	5%	3		
Ara-C, Vincristine and mitoxantrone	1	5%	2		
Cyclophosphamide + methotrexate	1	5%	1		
Daunorubicin/cytarabine	1	5%	2		
R-CHOP	1	5%	1		
Trastuzumab	1	5%	13–18		

Table 3
Behavioral performance on both paradigms. Median, minimum and maximum response time, for correct responses, is summarized for both groups, as well as number of missed and incorrect responses. Response times are calculated per subject as their median response time. A miss is defined as no response or a response before 150 ms or after 2 s. The effect of group on each parameter is assessed using Mann-Whitney U-test. Significant results (*p < .05, uncorrected*) are indicated in bold. GA: gestational age. Min: minimum. Max: maximum.

		Prenatal-exposed group			**Control group**			**Group effect**
		Median	Min	Max	Median	Min	Max	p-value
Go/Nogo								
Incorrect (%)		10.4%	4.2%	37.5%	12.5%	0%	29.2%	0.640
Miss (%)		0.5%	0%	14.6%	0%	0%	9.4%	0.211
Response time (ms)		562	406	763	534	429	739	0.149
Posner								
Miss (%)		2.6%	0%	7.6%	0.9%	0%	10.4%	0.056
Incorrect (%)		0.9%	0%	9.1%	0.3%	0%	2.1%	**0.023**
Response time (ms)								
No cue		534	459	665	501	404	611	0.076
Exogenous cue	Valid	429	356	625	399	335	481	**0.033**
	Invalid	519	450	654	485	369	541	**0.005**
Endogenous cue	Valid	421	362	630	392	312	457	**0.023**
	Invalid	490	408	698	439	375	519	**0.003**

[0%–≤6.6%] for all conditions) and Nogo (median = 0%, [0–8.33%]) trials. This was slightly elevated in the Go-trials (median = 13.54%, [7.29–20.83%]), which can be explained by motion often coinciding with the go-response. None of the Channels later used in analyses had to be interpolated for the Go/Nogo paradigm and occurred only rarely in Posner runs (median = 0/5 and maximum 2/5 channels per run).

Grand averages and significant group differences in time for the Go/Nogo paradigm are depicted in Fig. 1 and Table 4. Significant group effects (prenatal-exposed versus control group) are found centrally (456–546 ms) and parietally (456–574 ms, 638–648 ms and 942–958 ms), both indicating lower amplitudes in prenatal-exposed children compared to controls, mostly overlapping the P3 wave. No significant group-by-condition interactions were found. In the prenatal-exposed group two early main effects of GA were found frontally (164–182 ms) and parietally (52–82 ms). Lower/more negative values were observed with longer GA in the control group for both frontal (436–490 ms) and central (438–488 ms) clusters, which coincides with the later part of the N2 wave. Additionally, in this group, a late interaction effect of GA by condition was observed parietally (874–914 ms).

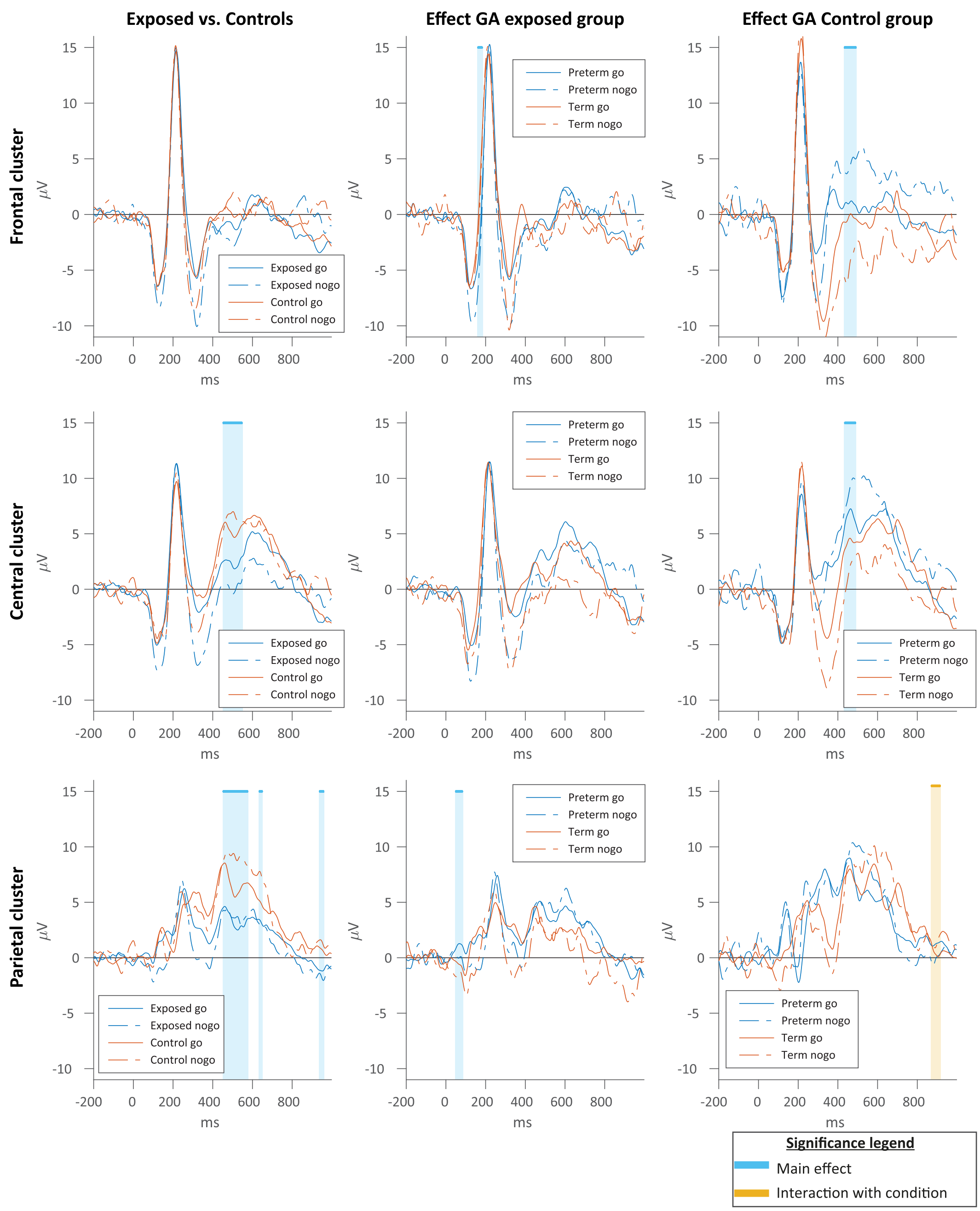

Fig. 1. Event-related potentials of the Go/Nogo paradigm. Left column shows the average responses in the 3 electrode clusters of interest (frontal, central and parietal, respectively in rows 1, 2 and 3) for both prenatal-exposed and control groups. Significant differences ($p < .05$, Bonferroni corrected for 3 clusters, min. 10 ms) between both groups, are highlighted in blue, and significant interaction effects of group (i.e. exposed/controls) by condition (i.e. go/nogo) in yellow. The middle and right column show the average responses, respectively in the prenatal-exposure and control groups, for the preterm and term children. Significant differences with gestational age are highlighted in blue, and significant interaction effects of gestational age by condition (i.e. go/nogo) in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
List of all significant time intervals in the event-related potentials of both paradigms. GA: Gestational age.

Electrode cluster	Cue type	Contrast	Significant time interval [ms]
Go/Nogo			
Frontal		Linear positive main effect of GA in the exposed group	164–182 ms
		Linear negative main effect GA in the control group	436–490 ms
Central		Main effect of exposed < control group	456–546 ms
		Linear negative main effect of GA in the control group	438–488 ms
Parietal		Main effect of exposed < control group	456–574 ms, 638–648 ms, 942–958 ms
		Linear negative main effect of GA in the exposed group	52–82 ms
		Interaction GA by cue validity in the control group	874–914 ms
Posner			
Parietal	Exogenous	Main effect of exposed < control group	204–216 ms
		Linear negative main effect of GA in the exposed group	430–456 ms
		Interaction GA by cue validity in the exposed group	864–900 ms
		Linear negative main effect of GA in the control group	130–150 ms
	No	Main effect of exposed < control group	472–568 ms
Occipital	Exogenous	Main effect of exposed < control group	452–548 ms
		Linear negative main effect of GA in the exposed group	412–472 ms, 692–742 ms
		Interaction GA by cue validity in the exposed group	390–408 ms, 426–470 ms, 706–732 ms, 864–900 ms
	Endogenous	Main effect of exposed < control group	454–492 ms
		Interaction GA by cue validity in the exposed group	508–528 ms, 860–888 ms
	No	Main effect of exposed < control group	522–538 ms, 550–566 ms
		Linear negative main effect of GA in the exposed group	604–624 ms, 666–694 ms

Figs. 2 and 3 show the grand averages of the Posner ERPs, respectively for the parietal and occipital clusters. The significant differences in time are detailed in Table 4. Main effects of group, with lower amplitudes in the prenatal-exposed group compared to controls, were observed: parietally for the exogenous cued (204–216 ms) and uncued (472–568 ms) conditions, and occipitally for the exogenous cued (452–548 ms), endogenous cued (454–492 ms) and uncued (522–538 ms and 550–556 ms) conditions, all but the first overlapping the pSW. Main effects of GA within the prenatal-exposed group were observed both parietally for the exogenous cued condition (430–456 ms) and occipitally for the exogenous (414–472 ms and 692–742 ms) and uncued (604–624 ms and 666–694 ms) conditions, all indicating a more positive amplitude with higher prematurity in the pSW. In the same group, interaction effects of GA by cue validity were found parietally for the exogenous cued condition (866–900 ms) and occipitally for both exogenous (390–408 ms, 426–470 ms, 706–732 ms and 864–900 ms) and endogenous (508–528 ms and 860–888 ms) cued conditions, all indicating higher potentials for the incorrect compared to correct cued trials with higher prematurity. All but the last cluster were located within the pSW. One early parietal effect of GA in the control group was observed in the exogenous cued condition (130–150 ms).

4. Discussion

This study investigated the impact of prenatal exposure to chemotherapy on the development of executive functioning, and the contribution of late-prematurity to this effect, through the use of ERP. In the Go/Nogo paradigm (Fig. 1 and Table 4), lower P3 amplitudes were found in central and parietal clusters for prenatal-exposed children, compared to controls, indicating an effect on response inhibition. Using the same paradigm, shorter gestation at birth in the control group was correlated with a less negative signal in the late fronto-central N2 component, indicating an effect of late-prematurity on conflict monitoring. In the Posner paradigm (Figs. 2, 3 and Table 4), lower pSW amplitudes were found in the prenatal-exposed group compared to controls, indicating an impact on cognitive resources that are required for response selection and cognitive model updating. Moreover, this outcome was further empowered by a slower response time to all cued conditions, as well as a higher incorrect rate in the prenatal-exposed group compared to controls. Within the prenatal-exposed group GA negatively correlated with pSW amplitudes as well as larger discrimination in the pSW amplitude between valid and invalid cued trials. Additionally, in the Posner paradigm, an early effect was found for prenatal-exposed children compared to control children, as well as with prematurity in the prenatal-exposed group. Though these effects could indicate changes in task detection, these results should be carefully interpreted as these early components are highly affected by the more pronounced P3 component.

The lower Go/Nogo P3 amplitude, observed in the prenatal-exposed group, has similarly been observed by Boucher et al. after prenatal exposure to tobacco (Boucher et al., 2014). This P3 wave is related to response inhibition and cognitive resources for task execution (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004; Harper et al., 2014). On the other hand Boucher et al. found both prenatal exposure to tobacco and childhood exposure to several contaminants to be correlated with a less negative N2 (Boucher et al., 2012, 2014), which is related to conflict monitoring. Here we only observed a more negative late N2 peak with higher GA in control children, indicating that both prematurity and prenatal exposure might have an effect on conflict monitoring.

In the Posner paradigm prenatal-exposed children demonstrated delayed response times, more incorrect responses, and a lower pSW amplitude, which all indicate an effect of prenatal exposure to chemotherapy on spatial attention. Reorientation of spatial attention is an essential process for developing cognitive flexibility and creative thinking (Karbach and Unger, 2014). Hence, development of these cognitive skills might be impacted as well.

Within the prenatal-exposed group, the pSW in the Posner paradigm showed to be further lowered with longer gestation. Moreover, the observed difference in pSW amplitude between valid and invalidly cued conditions was smaller in this group with longer gestation. However, this effect of prematurity is not observed in the control group, indicating that this observation is not directly related to prematurity. Rather, this observation might result from other effects, such as differences in cumulative chemotherapy doses, chemotherapy types and treatment timing with regards to the fetal development. Similarly, cancer diagnosis

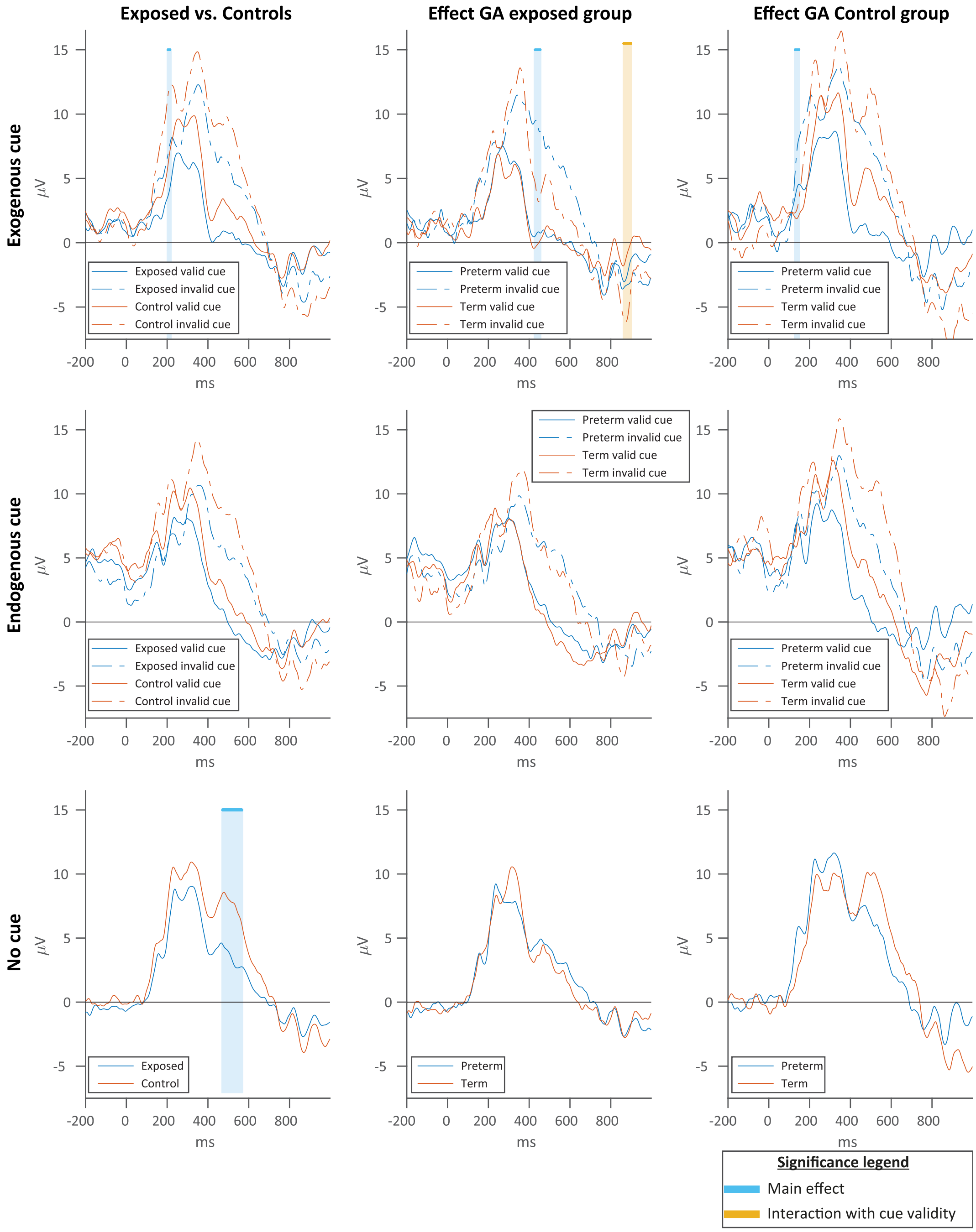

Fig. 2. Parietal event-related potentials of the Posner paradigm. Left column shows the average responses of each cue type (exogenous, endogenous and no cue, respectively in rows 1, 2 and 3) for both prenatal-exposed and control groups in the parietal electrode cluster. Significant differences ($p < .05$, Bonferroni corrected for 2 clusters, min. 10 ms) between both groups, as indicated by RM-ANOVA, are highlighted in blue, and significant interaction effects of group (i.e. exposed/controls) by cue validity in yellow. The middle and right column show the average responses, respectively in the prenatal-exposure and control groups, for the preterm and term. Significant differences with gestational age, as indicated by RM-ANOVA, are highlighted in blue, and significant interaction effects of gestational age by cue validity in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

can induce stress and anxiety, impacting fetal neurodevelopment. This impact of prenatal stress on neurodevelopment has earlier been found to be dependent on its timing during pregnancy (Van den Bergh et al., 2017).

While current literature observed a higher incidence of prematurity and SGA after prenatal exposure to cancer therapy, cancer therapy during pregnancy has not been found to impact the neurodevelopment of these children (Amant et al., 2012, 2015b; Cardonick et al., 2015). However, these studies focused on IQ as an indicator for neurodevelopment, which was also not found to be significantly different between groups in this study ($p = .15$). To our knowledge, this study is the first to investigate a link between prenatal exposure to chemotherapy and the development of executive functioning. This suggests that although prenatal exposure to cancer treatment is not necessarily observed in IQ-scores obtained early in life (Amant et al., 2012, 2015b; Cardonick et al., 2015), specific cognitive skills which develop later in childhood and adolescence, such as executive functioning, might be affected in later life.

Neuropsychological studies demonstrated preterm birth to affect executive functioning later in life, including processes of

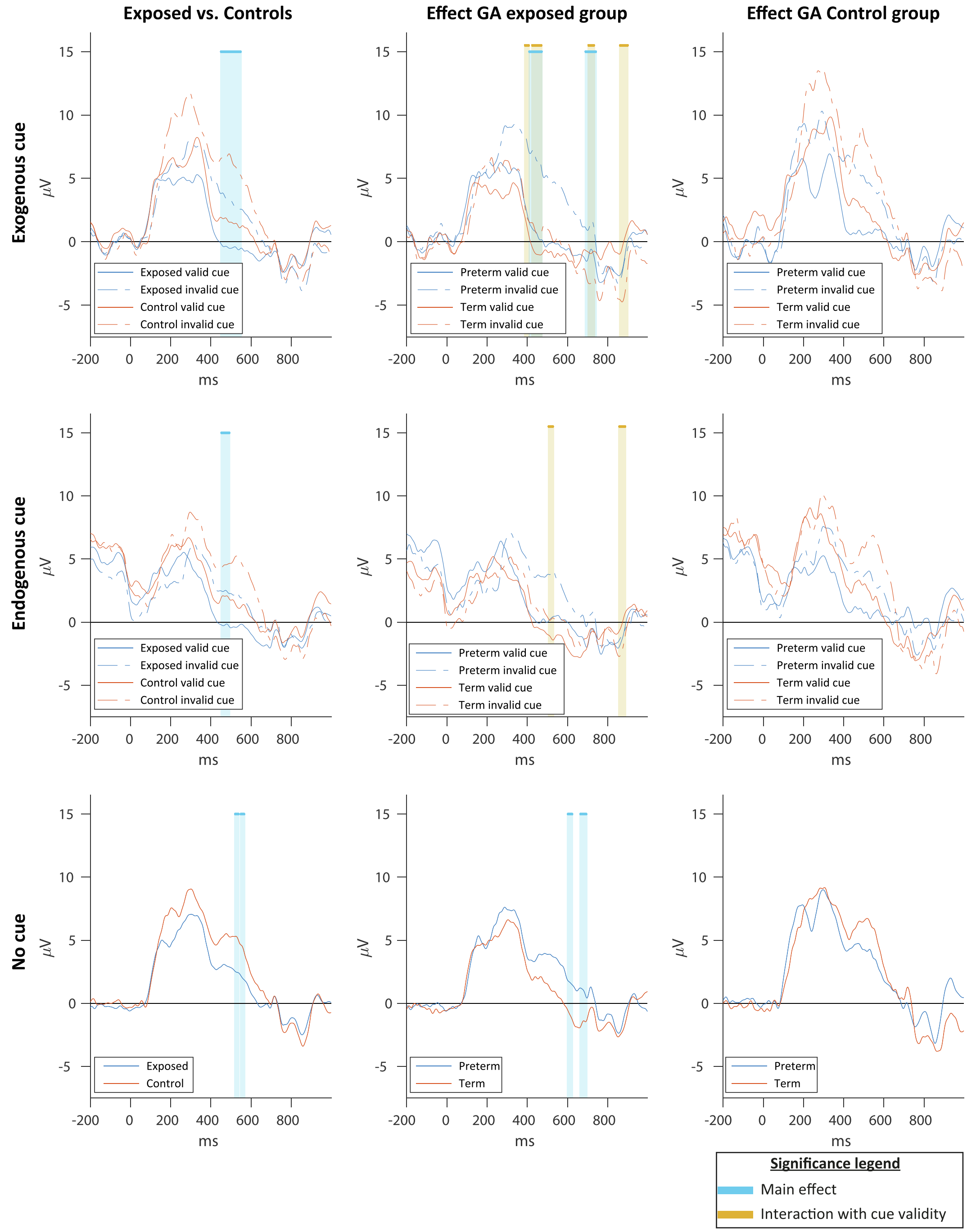

Fig. 3. Occipital event-related potentials of the Posner paradigm. Left column shows the average responses of each cue type (exogenous, endogenous and no cue, respectively in rows 1, 2 and 3) for both prenatal-exposed and control groups in the occipital electrode cluster. Significant differences ($p < .05$, Bonferroni corrected for 2 clusters, min. 10 ms) between both groups, as indicated by RM-ANOVA, are highlighted in blue, and significant interaction effects of group (i.e. exposed/controls) by cue validity in yellow. The middle and right column show the average responses, respectively in the prenatal-exposure and control groups, for the preterm and term children. Significant differences with gestational age, as indicated by RM-ANOVA, are highlighted in blue, and significant interaction effects of gestational age by cue validity in yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

inhibition and cognitive flexibility (van Houdt et al., 2019). In this study we observed an effect of prematurity on conflict monitoring in a Go/Nogo experiment, but not on spatial attention. However, 15/22 premature children, included in current study, are born moderate to late preterm, which remains an understudied population in current literature (van Houdt et al., 2019). Moreover, several common comorbidities of preterm born children, which were explicitly excluded in the current study, might partially explain the deviation of our findings from previous research. Both these factors and the limited sample size of the current study might explain the more subtle nature of the observed findings regarding prematurity.

Current guidelines in oncological treatment during pregnancy advise to, whenever feasible, treat cancer during pregnancy in favor of a longer gestation (Amant et al., 2015a). However, this study found response inhibition and spatial attention to be affected in children that were prenatally exposed to chemotherapy, while this was not correlated to (late-)prematurity. These findings, on their own, are not a contra-indication for chemotherapy administration during pregnancy. However, it does indicate that further research is necessary on the long-term impact of chemotherapy during pregnancy to re-inform clinical practice on the costs and benefits of late-premature induction over treatment during pregnancy.

Some limitations in this study should be mentioned. First, cancer in pregnancy is a heterogenous pathology, resulting in a heterogeneous treatment. As a consequence, this study cannot discriminate whether some cancer pathologies and treatments contribute more to the observed effects. Furthermore, cancer diagnosis and treatment during pregnancy might affect neurocognitive development through a multitude of direct and indirect pathways (Vercruysse et al., 2016). The current study cannot discriminate the contributions of individual pathways to the observed effect. However, by excluding major obstetrical and neonatal complications, we try to control for effects on maternal health that are not caused by the cancer diagnosis or treatment. Next, due to the relative rare occurrence of cancer in pregnancy, we acquired data during a relative long period of time and only recruited 20 prenatal-exposed children. However, the testing set-up remained unchanged during the whole testing period. Moreover, we used a priori knowledge from literature to limit multiple testing and age effects were limited by testing at a very narrow age-range (8.79–9.91y).

5. Conclusions

To our knowledge, this study is the first to find an effect of prenatal exposure to chemotherapy on the development of executive functioning, which was not limited to the effect of late-prematurity. This further emphasizes the need for a long-term follow-up of prenatal-exposed children, as these cognitive functions will further develop throughout adolescence (Karbach and Unger, 2014). Furthermore, multi-disciplinary and multi-modal approaches will be essential in understanding the neurocognitive extent and neurobiological substrate of prenatal exposure to chemotherapy. Though the observed effects in this study are relatively subtle, the authors believe this will further guide clinical decision-making and will enable physicians to better inform patients, eventually contributing to a better treatment and follow-up of cancer in pregnancy.

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Declaration of Competing Interest

All authors report no disclosures.

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