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Altered orbitofrontal activation in preterm-born young adolescents during performance of a reality filtering task

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ABSTRACT

Preterm birth is one of the main causes for neurodevelopmental problems, and has been associated with a wide range of impairments in cognitive functions including executive functions and memory. One of the factors contributing to these adverse outcomes is the intrinsic vulnerability of the premature brain. Neuroimaging studies have highlighted structural and functional alterations in several brain regions in preterm individuals across lifetime. The orbitofrontal cortex (OFC) is crucial for a multitude of complex and adaptive behaviours, and its structure is particularly affected by premature birth. Nevertheless, studies on the functional impact of prematurity on the OFC are still missing.

Orbitofrontal Reality filtering (ORFi) refers to the ability to distinguish if a thought is relevant to present reality or not. It can be tested using a continuous recognition task and is mediated by the OFC in adults and typically developing young adolescents. Therefore, the ORFi task was used to investigate whether OFC functioning is affected by prematurity. We compared the neural correlates of ORFi in 35 young adolescents born preterm (below 32 weeks of gestation) and aged 10 to 14 years with 25 full term-born controls.

Our findings indicate that OFC activation was required only in the full-term group, whereas preterm young adolescents did not involve OFC in processing the ORFi task, despite being able to correctly perform it.

1. Introduction

Preterm birth, defined as when delivery happens before 37 full weeks of gestational age (GA), affects an estimated 11.1% of all live births every year (Blencowe et al., 2013). It has been associated with a wide range of impairments in cognitive functions and is one of the predominant risk factors for neurodevelopmental problems (Twilhaar et al., 2018), affecting executive functions such as memory and attention (Rommel et al., 2017; Allotey et al., 2018; Costa et al., 2017; Burnett et al., 2018) and affective behaviour (Hornman et al., 2016), among others (Moreira et al., 2014; Allotey et al., 2018). Crucially, although some of these difficulties are often unveiled only when children reach school age, it has been shown that they may persist throughout life (Anderson, 2014; Kajantie et al., 2019). Factors contributing to these detrimental consequences include the intrinsic vulnerability of the premature brain. Understanding the neurological underpinnings of these difficulties is paramount to identify potential interventions and establish critical periods to restore typical development (Wolke et al., 2019).

One of the brain regions that deserve special attention in the context of prematurity is the orbitofrontal cortex (OFC). It is crucial for a variety of complex and adaptive behaviors, such as executive abilities including assignment of value to a specific stimulus (Montague and Berns, 2002), prediction of specific outcomes (Rudebeck and Murray, 2014), reward processing (Kahnt, 2018), as well as decision making (Bechara, 2000; McClure et al., 2004). Additionally, it is implicated in social cognition and appropriate social behavior (Rolls, 2004; Jonker et al., 2015), including affect recognition and emotional reappraisal (Blair, 2000; Adolphs, 2001; Wager et al., 2008; Dixon et al., 2017), and hedonic experiences (Kringelbach, 2004). As part of the prefrontal cortex, the

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OFC has a critical period of development in the last trimester of pregnancy (Huttenlocher and Dabholkar, 1997; Ruoss et al., 2001). Therefore, OFC maturation is impacted by preterm birth, which usually takes place during this delicate period. As a consequence, several of the abilities mentioned above are defective in the preterm population. Various studies reported a reduced capacity to recognize and regulate emotions (Hall and Wolke, 2012; Johnson and Marlow, 2011) and an impairment in the ability to learn reward associations (Espy et al., 2002; Duerden et al., 2016) in preterm infants and children, compared to full-term peers. The preterm brain can be characterized by brain volume reduction specifically in the OFC (Thompson et al., 2007). A reduction in the secondary sulci depth of the OFC, together with a reduced gray matter volume in the same region has been found in very preterm children (Gimenez et al., 2006). Fischi-Gómez et al. (2015) found altered connectivity (i.e,; decreased fractional anisotropy) in the orbitofrontal and the medial prefrontal network in extreme preterm children, and this weakness correlated with impaired social skills, simultaneous processing and hyperactivity. Cortical thickness in the frontal area, including OFC, has been correlated with internalizing and externalizing behavioral problems, common in premature children (Zubiaurre-Elorza et al., 2012). In addition, adolescents born preterm showed altered distribution of the orbitofrontal sulcogyral folding pattern, which correlated with deficits in executive functions (Ganella et al., 2015). More recently, a link between lower gestation age and reduced volume in brain regions including OFC was found (Nassar et al., 2019). Taken together, all these data highlight the particular vulnerability of the OFC structure in the brain of individuals who were born prematurely. While preterm birth has been shown by several neuroimaging studies to be linked to structural and connectivity alterations in the prefrontal cortex and especially the OFC (Gimenez et al., 2006; Bjuland et al., 2013; Nosarti et al., 2014; Sripada et al., 2018), to the best of our knowledge studies investigating OFC function are still missing in this context. The aim of our study was thus to fill this gap, using a task that specifically taps into this region while recording the functional activation of the brain in preterm-born young adolescents, and then comparing them to term-born peers.

The task used to specifically activate the OFC was the Orbitofrontal Reality Filtering task (ORFi, Schnider, 2018). ORFi is a thought control mechanism necessary for synchronizing thought and behavior with ongoing reality (Schnider, 2018; Schnider, 2003). Adult subjects failing in this capacity confuse their current role, are disoriented, confabulate and act on the basis of memories that do not relate to current reality (Schnider and Ptak, 1999). In children, ORFi is already functional at the age of 7, and then continuously develops into adulthood in parallel with the ability to store new information (Liverani et al., 2017). This memory mechanism can be assessed using repeated runs of a continuous recognition task composed of the same set of pictures presented in a different order within each run. Participants are asked to indicate picture recurrence only within the ongoing run.The first run of the task assesses recognition memory and can be done on the basis of familiarity alone. Schnider and colleagues found activation of the hippocampal area in the this first run of the task (Schnider et al., 2000). The second run of the task is composed of the same images. Thus, all the pictures are already known, and the sense of familiarity is not sufficient to correctly perform the task. This run requires the ability to sense whether familiarity emanates from a previous appearance of an items within the "ongoing reality" of the current run (Schnider et al., 1996; Schnider and Ptak, 1999). Reality-confusing patients fail to suppress the interference of items that appear for the first time within this second run; their false positive rate increases. (Schnider et al., 1996; Schnider and Ptak, 1999). The first description of this mechanism was based on the observation of patients suffering from confabulations and disorientation, whose task performance was characterized by a remarkable increase of false positives in the second run (Schnider et al., 1996; Schnider and Ptak, 1999; Nahum et al., 2012). Lesion analysis on these patients revealed that ORFi depends on the OFC and on structures directly connected with it (Schnider et al., 1996; Schnider, 2018). Functional imaging studies corroborated this hypothesis in adults (Treyer et al., 2003; Treyer et al., 2006) and in typically developing young adolescents aged 10–14 years old, with significantly increased bilateral OFC activation during ORFi processing (Liverani et al., 2020). In the present study, we aimed to investigate the preterm children' s ability to perform the ORFi task and to compare the OFC activation of this population to term-born controls. As already mentioned above, prematurity has a proven detrimental effect on OFC volume and connectivity, and these alterations are associated with impaired behavioral outcomes. This suggests a possible alteration of this structure also from a functional point of view in the preterm population. Therefore, we hypothesized that the activation of the OFC in the preterm population should be lower than in controls. We also wanted to explore whether compensation mechanisms have been put in place in order to balance the negative effect of prematurity on the OFC region.

2. Methods

2.1. Participants

Study participants underwent a baseline MRI assessment in the context of a study on the effect of a mindfulness based intervention on very preterm adolescents, described in detail elsewhere (Siffredi, Liverani et al., https://www.medrxiv.org/content/10.1101/2021.01.19.21250087v1). Since meditation is known to improve executive functions and emotional competencies, we targeted adolescence as a key developmental window that has been shown to be associated to executive and socio-emotional dysfunctions. Young adolescents born before 32 gestational weeks (between 01/01/2003 and 31/12/2008) in the Neonatal Unit and followed up at the Division of Child Development and Growth at the Geneva University Hospital, in Switzerland, were invited to participate. Young adolescents with severe sensory or physical disabilities (cerebral palsy, blindness, hearing loss), with an intelligence quotient below 70 or who did not speak French were excluded. Thirty-seven 10—14 year-old very preterm-born (PTB) individuals (20 females, mean age 12.1 $\pm$ 1.2 years) thus joined the study. In order to estimate general intellectual functioning, the General Ability Index (GAI) from the Wechsler Intelligence Scale for Children - 4th edition (WISC-IV, Wechsler, 2014; Wechsler, 2014) was used. Participants scored within the normal range of intellectual functioning. There was no significant difference between preterm adolescents enrolled in the study and those who refused to participate in terms of birth weight, gestational age, head circumference and presence of brain lesions linked to cystic periventricular leukomalacia. Nevertheless, there was a significant difference for multiple births, with a higher number of multiple births in the group enrolled in the MBI study compared to the group who refused to participate. In regard to demographic characteristics, there was no group difference in terms of gender. Nevertheless, there was a significant group difference in parents' socio-economic status, as assessed by the Largo's questionnaire (Largo et al., 2008), with significantly higher socio-economic status in the group enrolled in the MBI study compared to the group who refused to participate. Concerning brain alterations, five out of 35 preterm adolescents had intraventricular hemorrhage after birth, and one had periventricular leukomalacia. No other known brain abnormalities were reported in our sample. Twenty-seven age-matched healthy term-born (TB) early adolescents (12 females, mean age 12 $\pm$ 1.01 years) were recruited through advertisements. One TB participant was excluded due to strong signal distortions on fMRI images caused by the subject's dental braces. One TB and two PTB participants were excluded due to high head-motion. Twenty-five TB and thirty-five PTB participants were finally included in the analysis.Cohort characteristics are detailed in Table 1. The Ethics Committee of the Canton of Geneva approved the study, which was carried out in accordance with the Declaration of Helsinki. Caregivers and participants provided informed written consent. All participants received a gift voucher of 100 Swiss francs for their participation in the study upon completion of the

Table 1
Cohort characteristics. *Note: GA = Gestational age, BPD = Bronchopulmonary dysplasia, IVH = intraventricular hemorrhage, PVL = periventricular leukomalacia.*

Group	Age in months (SD)	GA in weeks (SD)	Birth weight in grams (SD)	SES	BPD	IVH	PVL
Preterm	146.72 (13.6)	29.13 (1.9)	1201.9 (380.6)	3.92 (2.4)	5 (14%)	5 (14%)	1 (2.8%)
Control	143.6 (12)	39.60 (1.7)	3435.6 (443.1)	3.24 (1.6)	0	0	0

protocol.

2.2. Experimental Paradigm

All participants performed the reality filtering task illustrated in Fig. 1, from Liverani et al., 2020, associated with an event-related fMRI paradigm. In short, subjects performed two runs of a continuous recognition task in which a sequence of animal images were shown, and were asked to identify animals that had already been seen within the current run. Images shown for the first time within the first run were called "Distractors 1" (D1, n = 30), while images seen for the second time within the first run were called "Targets 1 " (T1, n = 30). Images shown for the first time within the second run were called "Distractors 2" (D2, n = 30), while images seen for the second time in the second run were called "Targets 2"(T2, n = 30). The two runs were separated by a 3-min break. Participants had an MRI-compatible mouse in their right hand and were asked to press the first button (i.e, the left button) for the Distractors (i.e., images seen for the first time in the run) and the second button (i.e., the right button) for the Targets (i.e., images seen for the second time in the run). The set of images used in both runs was the same, meaning that the second run has the added difficulty of inhibiting the recognition of images seen in the previous run. Therefore, the ability to accurately perform the second run relied on the correct functioning of the ORFi mechanism. Pictures were a set of 30 cartoon drawings of animals and were presented for 5 s on the screen. Picture repetition occurred after 6—9 intervening images. Each picture was presented twice. After each image, a fixation cross was presented during between 1440 and 2400 ms. Each run lasted approximately 7.5 min. Stimuli were displayed on a white screen at the head of the scanner via a 45 angled mirror fixed to the MRI head coil. Task programming, stimuli display and response logging were done using E-Prime 2 (Psychology Software Tools, Pittsburg, USA). All participants completed a short training in the mock scanner using a different set of images before the MRI.

2.3. Behavioral data analysis

Behavioral analysis on the ORFi task were based on accuracy (i.e., number of correct answers) and reaction time for each condition and each run (Distractors in run 1 = D1, Targets in run 1 = T1, Distractors in run 2 = D2, Targets in run 2 = T2). A 2 × 2 × 2 repeated measures analysis of variance (ANOVA) was performed on accuracy and reaction time with the within-subject factors run (1, 2) and condition (Distractors, Targets) and the between subject factor group (preterm children, term-born children).

2.4. Image acquisition

MRI data were recorded on a Siemens 3T Magnetom Prisma scanner at Campus Biotech, Geneva, Switzerland. Structural T1-weighted MP-RAGE (Magnetization Prepared Rapid Gradient Echo) sequences were acquired using the following parameters: voxel size = 0.9 × 0.9 × 0.9 mm; repetition time (TR) = 2300 ms; echo time (TE) = 2.32 ms; inversion time (TI) = 900 ms; flip angle (FA) = 8°; field of view (Fov) = 240 mm. Functional images were T2*-weighted with a multislice gradient-echo-planar imaging (EPI) sequence of 64 slices; voxel size = 2 x 2 x 2 mm; TR = 720 ms; TE = 33 ms; Fov = 208 mm. Finally, a fieldmap was acquired each time a participant entered the scanner, with TR = 627 ms; TE1 = 5.19 ms; TE2 = 7.65 ms; and FA = 60°.

2.5. MRI data preprocessing

Our data were preprocessed using SPM12 (Wellcome Department of Imaging Neuroscience, UCL, UK) in MATLAB R2016a (The MathWorks, Inc., Natick, Massachusetts, United States) as in Liverani et al., 2020.

One particular challenge in studying frontal brain areas using fMRI is the considerable vulnerability of these regions to signal distortions caused by field inhomogeneities around the air-filled sinuses (Gorno-Tempini et al., 2002). To correct for the resulting geometrical

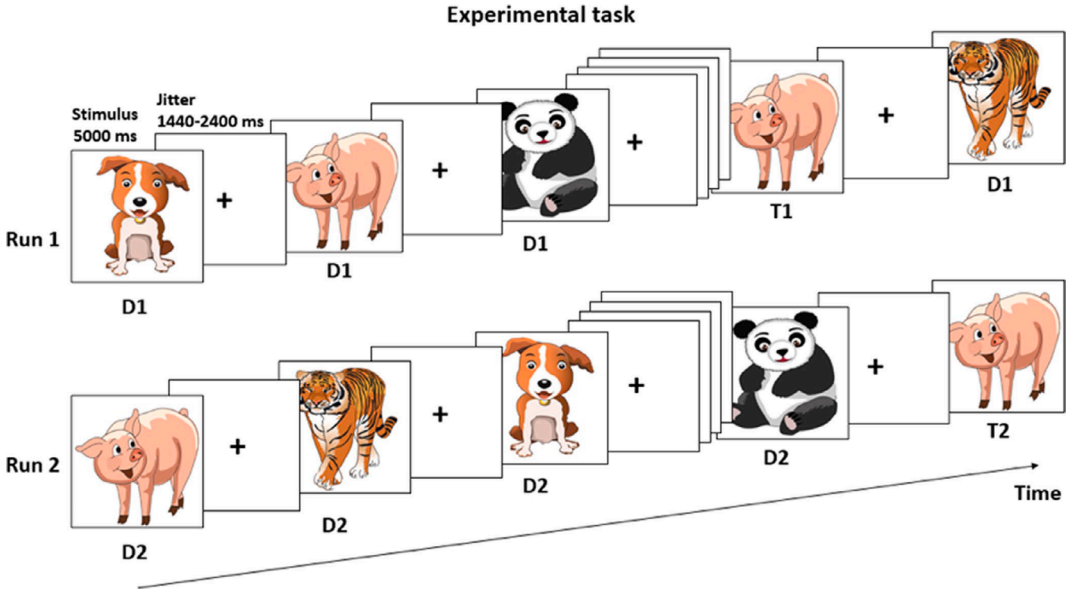

Fig. 1. Task design. The task was composed of 2 runs, separated by a break of 3 min. Distractors (D1, D2) are images presented for the first time within a run; targets (T1, T2), are images repeated within the same run. Figure from Liverani et al., 2020.

distortions, a field map was calculated from an additional stock double-echo field map sequence included in our MRI protocol (Hutton et al., 2002).

The fMRI images from each participant were spatially realigned and unwarped, respectively, to correct for motion artefacts and potential geometric distortions. The unwarping step brings two main advantages: it improves the co-registration between structural and functional images, and reduces the distortion variability across subjects during spatial normalization to a common space (Hutton et al., 2002). Functional images were then coregistered to structural images in subject space and smoothed with a Gaussian filter of full width at half maximum (FWHM) = 6 mm. To be able to perform a group level comparison, data were warped into MNI (Montreal Neurologic Institute) space via a study-specific DARTEL (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) template. Such normalisation methods have been shown to be robust to age differences in participants from the age of 7 (Ashburber and Friston, 1998; Burgund et al., 2002). In addition, including the DARTEL template as an intermediate step is among the top ranked currently available deformation algorithms (Klein et al., 2009).

2.6. Head motion

Head motion was assessed in terms of Framewise Displacement (FD; Power et al., 2014; Power et al., 2014). One TB and two PTB subjects for whom more than 20% of frames would be affected by motion (that is, frames with FD > 0.5 mm, one frame before, and two after those) were excluded. For the remaining subjects, total head motion was quite low in both groups: In the control group, for the first fMRI run the mean FD per frame was 0.159 mm with a standard deviation (SD) of ± 0.05 mm; for the second run the mean FD was 0.154 mm ± 0.05 mm; in the preterm group, for the first fMRI run the mean FD per frame was 0.163 mm with a standard deviation (SD) of ± 0.05 mm; for the second run the mean FD was 0.165 mm ± 0.06 mm. The two groups did not significantly differ in mean FD neither for run 1 (unpaired t-test, p = 0.74) nor for run 2 (p = 0.54).

2.7. fMRI analysis

Whole brain analysis: The fMRI data were analysed using SPM12 (Wellcome Department of Imaging Neuroscience, UCL, UK) in MATLAB R2016a (The MathWorks, Inc., Natick, Massachusetts, United States). For each subject, we built a first-level General Linear Model (GLM) including the condition (Distractor or Target images) regressors, as well as regressors of no interest that might affect the signal. Specifically, to account for effects potentially caused by head motion, we included in our model covariates-of-no-interest calculated in the following fashion: first, we computed the 24-parameter Volterra Expansion (VE) of the 6 motion parameters stored during the realignment step of the pre-processing pipeline. Secondly, we extracted the top 6 components (or those that explained 95% of the variance in the VE) via singular value decomposition (SVD). Then, we included these components as nuisance regressors in the subject-level design matrix. This approach has been successfully used on our previous analyses of child data (Adam-Darque et al., 2018; Liverani et al., 2020). Finally, we employed the scan-nulling strategy (Lemieux et al., 2007) to ignore information contained in fMRI images in which FD > 0.5 mm, by adding extra regressors-of-no-interest for each of these time points. Finally, the results from this first-level analysis were included in a second-level factorial model including run and condition as factors. Within the condition factor, correct and incorrect answers were modelled together due to the extremely low rate of incorrect ones. Statistical analysis was performed on a voxelwise basis searching for run, group, or interaction effects.

Region of interest (ROI) analysis: Given the known involvement of the orbitofrontal cortex in the Reality filtering task studied here (Schnider, 2018; Liverani et al., 2020), we have delved deeper into the analysis of this area as a region of interest (ROI). To avoid confounding the results, the ROI we selected was based on a mask obtained from Neurosynth.org using a combination of 666 independent studies that included the OFC. Group, run and condition effects were analysed using Student's t-tests. Interactions involving any combination of the three were analysed using a factorial analysis of variance (ANOVA).

3. Results

3.1. Participants

The preterm group and the control group did not differ in term of sex, age at the assessment and socio-economic status (all $p > .05$). Nevertheless, there was a significant difference for the general ability index (GAI) as measured using the WISC-IV, with control participants scoring higher than the preterm ones ($t_{59} = -2.9$, $p = 0.006$). Furthermore, a significant difference were found in term of gestational age and weight at birth ($t_{59} = -22$, $p < .001$ and $t_{59} = -20.8$, $p < .001$, respectively), with preterm children having lower values compared to their term-born peers, as expected.

3.2. Behavioral results

For each group, the mean of accuracy, reaction time and false positive for each condition and each run are reported in Table 2. Analysis on accuracy revealed a significant main effect of condition, with higher correct responses for Distractors compared to Targets ($F_{(1)} = 6.93$, $p = .011$, $\eta^2 = 0.1$). Concerning reaction times, a main effect of run was found ($F_{(1)} = 30.14$, $p < .001$, $\eta^2 = 0.01$), with faster responses in run 1 compared to run 2.

3.3. Comparison of whole-brain activation during the two task runs

Since both groups were able to successfully perform the ORFi task, we started out by investigating whether the difference in activation between the two runs would be similar in our entire cohort to what was seen in controls (Liverani et al., 2020). In order to investigate the general differences in activation between the two runs, we thus performed a second-level analysis where all the participants from both groups were pooled together. These results are depicted in Fig. 2. During performance of run 2, three clusters were significantly more active than during run 1. These are: right superior parietal lobule (MNI coordinates x = −54 y = −18 z = 49; $p_{FWE-corr} = 0.001$), right amygdala (x = 21 y = −9 z = −18; $p_{FWE-corr} = 0.01$), and left amygdala (x = −21 y = −9 z = −18; $p_{FWE-corr} = 0.02$) – see Fig. 2A. During performance of run 1, the posterior parietal cortex was more activated (x = 0 y = −51 z = 20; $p_{unc} = 0.001$). This contrast can be seen in Fig. 2B.

3.4. Group comparison of whole-brain activation during the two task runs

We next sought to identify whether there was a group difference in activation during performance of the task runs. These results are illustrated in Fig. 3. Term-born controls had higher activation of the medial temporal gyrus (MNI coordinates x = −39 y = −39 z = 9; $p = 0.001$, *unc*) and the right orbitofrontal cortex (x = 21 y = 42 z = −9; $p_{FWE-corr} = 0.02$). *Post hoc* analysis of activation during the two individual runs indicates that this difference is due to increased activation of these regions in the term-born group, as opposed to decreased activity in the preterm group (not shown). Preterm participants showed higher activation in visual attention areas (x = 40 y = −74 z = 20; $p_{FWE-corr} = 0.04$) and motor areas related to finger movement (x = −42 y = −39 z = 66; $p_{FWE-corr} = 0.04$) as compared to controls. *Post hoc* analysis of activation during the two individual runs indicates that this difference is due to increased activation of motor regions in the preterm group, and decreased activation in attention areas in the term-born group.

Table 2
Descriptive statistics of behavioral results on the Orbitofrontal Reality Filtering task. *Note: D1 = Distractors of run 1, T1 = Targets of run 1, D2 = Distractors of run 2, T2 = Targets of run 2.*

	Accuracy (SD)				Reaction time (SD)			
Group	**D1**	**T1**	**D2**	**T2**	**D1**	**T1**	**D2**	**T2**
Preterm	28.8 (1.4)	28.2 (1.9)	28.6 (1.4)	27.8 (2.7)	1384.4 (314.17)	1432.7 (344.9)	1566.5 (389.6)	1518.2 (370.8)
Control	28.8 (1.3)	27.4 (4.9)	28.2 (1.8)	27.1 (4)	1437.6 (385.3)	1449 (354.2)	1573.9 (336.5)	1553.7 (397.4)

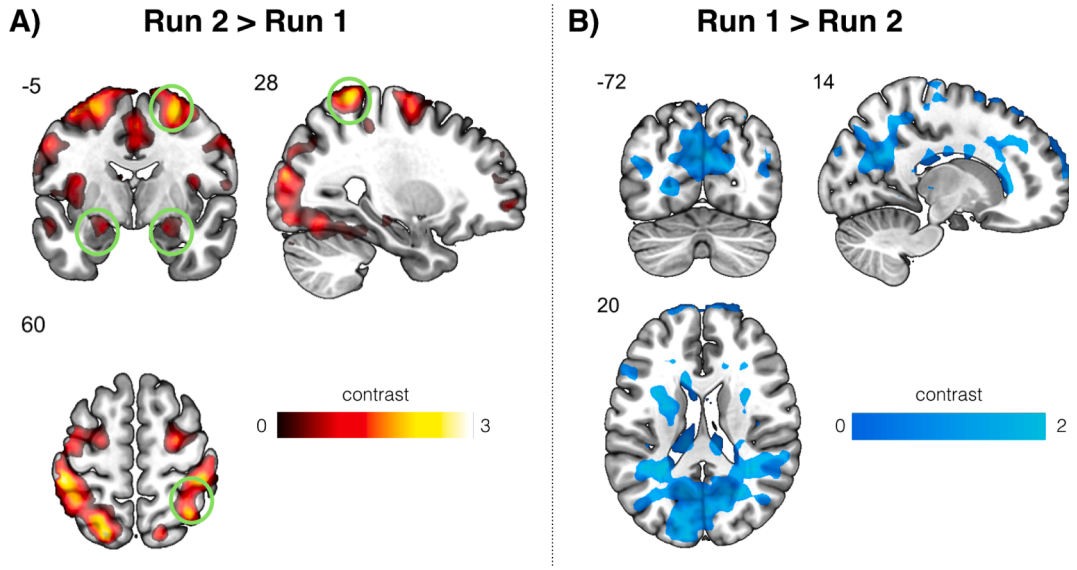

Fig. 2. Comparison between the whole brain activation of the two runs. The brain maps show regions that were most activated (at $p < 0.001$), with subjects from both groups pooled together. The brighter the color, the stronger the effect in the highlighted region. A) During run 2 (relevant for reality filtering), regions typically involved in external attention (e.g., superior parietal lobule) were more activated than during run 1. Green circles highlight regions that survived FWE correction at $\alpha = 0.05$. *Post hoc* analysis of activation during the two individual runs indicates that this difference is due to increased activation of these regions during run 2, as opposed to decreased activity during run 1. B) During run 1, regions that typically form networks involved in internally-oriented processes (*e.g.*, default mode network) are more highly activated. *Post hoc* analysis of activation during the two individual runs indicates that this difference is due to increased activation of these regions during run 1. Note that no regions were significantly more active during run 1 than during run 2 after FWE correction.

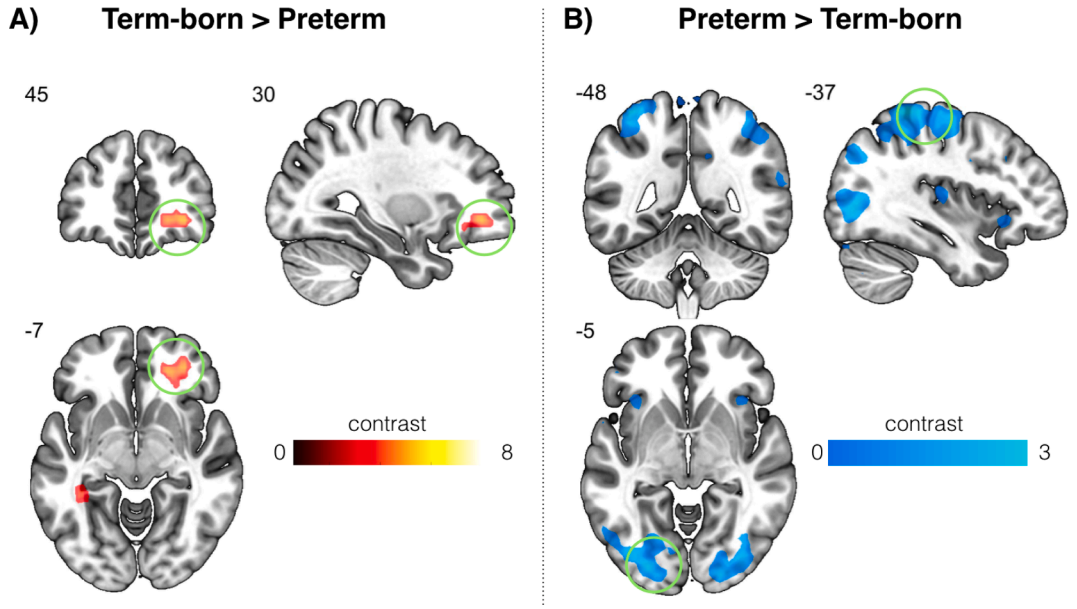

Fig. 3. Group differences in activation across the two runs. The brain maps show regions that were most activated, with maps from both runs pooled together. The brighter the color, the stronger the effect. Green circles highlight regions that survived FWE correction at $\alpha = 0.05$. A) Term-born controls had higher activation of the medial temporal gyrus (MNI coordinates x = −39 y = −39 z = 9; $p_{unc} = 0.001$) and the right orbitofrontal cortex (x = 21 y = 42 z = −9; $p_{FWE-corr} = 0.02$). B) Preterm participants showed higher activation in visual attention areas (x = 40 y = −74 z = 20; $p_{FWE-corr} = 0.04$) and motor areas related to finger movement (x = −42 y = −39 z = 66; $p_{FWE-corr} = 0.04$).

3.5. Interactions between group and run effects

A group versus run interaction contrast identified several clusters as depicted in Fig. 4. They include the right orbitofrontal cortex (x = 15 y = 39 z = −6; p_{unc} = 0.001), nodes of the frontoparietal network such as dorsolateral prefrontal cortex and posterior parietal cortex (x = −24 y = 30 z = 48; p_{unc} = 0.001), insula (x = −43 y = −3 z = −15; p_{unc} = 0.001) and visual attention areas (x = −27 y = −63 z = 21; p_{unc} = 0.001). A *post hoc* comparison between the two runs in the two groups separately revealed that these differences are mainly due to increased activation of these regions during the second run in the control group (Fig. 4, right).

3.6. Orbitofrontal cortex as an ROI

An ROI analysis focused on the orbitofrontal cortex (OFC) revealed a Run effect (t = 2.47, p = 0.007), where the activation during run 2 was higher than during run 1, and a tendency for a Group effect (t = 1.4, p = 0.05) with controls showing higher activation than preterms. Finally, OFC activation during presentation of Distractors in the second run (the one assessing ORFi) was higher in controls than in preterm-born individuals (t = 2.38, p = 0.01). The ANOVA analysis revealed the interactions shown in Fig. 5. OFC activation was higher in both groups during performance of the second run (RF 2), and higher in the full term-born (Control) group than in the preterm-born group during both runs, but the difference in activation between the two runs was larger in the Control group, as indicated by the steeper slope of the orange line in the Run vs. Group interaction plot from Fig. 5 (p = 0.52, *n.s.*). In addition, OFC activation was stronger during the presentation of both types of stimuli (Distractor, D; and Target, T) during the second run, and the difference in activation between runs was larger for stimuli of the Target type, as shown by the red dotted line in the Stimulus vs. Run interaction plot from Fig. 5 (p = 0.33, *n.s.*). Finally, the control group has a much steeper increase in activation during presentation of Distractor stimuli with respect to Target stimuli, as compared to their preterm peers (yellow line in the Group vs. Stimulus interaction plot from Fig. 5, p = 0.37, *n.s.*). The difference in activation between groups was higher for Distractor images than for Target images (green full line in the Stimulus vs. Group plot from Fig. 5). None of the interactions were statistically significant, but the trends identified here are discussed in the next session.

4. Discussion

With this study we aimed to investigate whether OFC functioning was impacted in a cohort of very preterm early adolescents. To do that, we used a continuous recognition task assessing ORFi, a memory mechanism that specifically relies on this brain region.

4.1. Behavioural results

Behaviorally, all participants had a very high accuracy rate, with no difference between preterm and term-born children. Concerning reaction times, all participants were faster in the first compared to the second run, which is consistent with previous studies (Liverani et al., 2016; Liverani et al., 2020). This confirms that the simple recognition of previously seen images within the first run is less time consuming and requires less cognitive effort than the distinction between images pertinent to the ongoing reality or not, for which the ORFi mechanism is required. The comparison of the general ability index (GAI) showed that control participants scored significantly better than the preterm ones, even if all our participants were in the normal range. Nevertheless, since task performance was comparable in the two groups, we do not believe that this difference in global cognitive development could have impacted the neural correlates associated to task's completion.

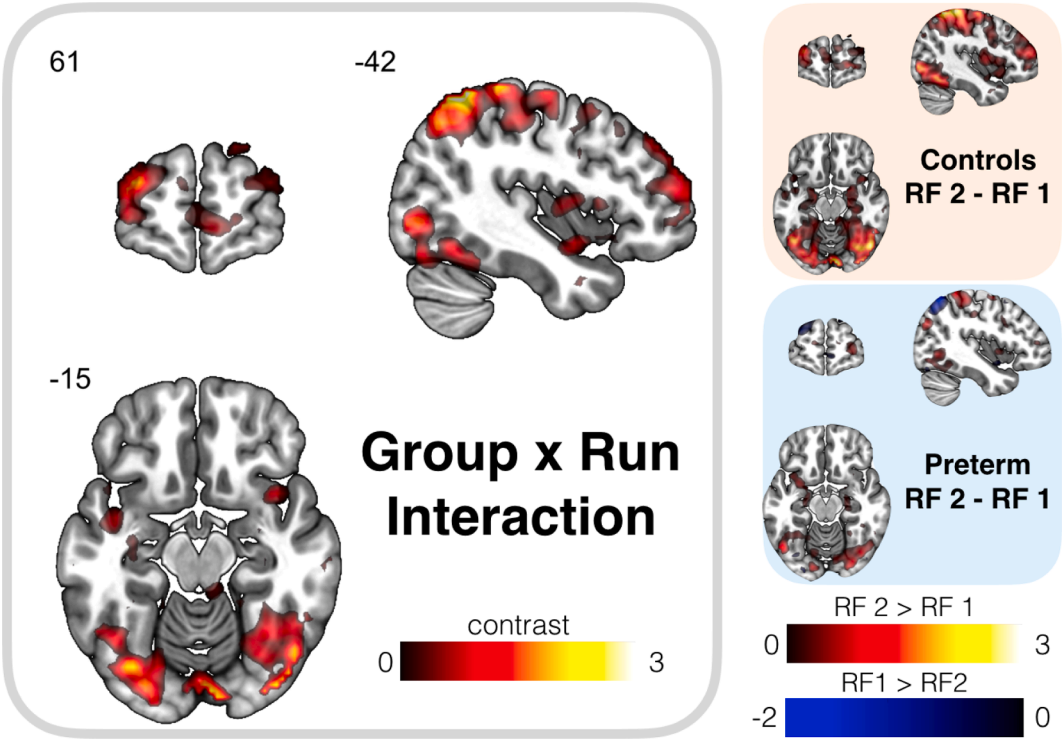

Fig. 4. Group versus Run interaction effects. Left: The brain maps show regions whose activation showed an interaction of Group and Run effects at height threshold p = 0.001. Brighter colors indicate stronger effects. Right, orange inset: Contrast between the two runs in the Control group. Red areas indicate higher activation during run 2 (RF 2), while blue regions indicate higher activation during run 1 (RF 1). Right, blue inset: Contrast between the two runs in the preterm group. Red areas indicate higher activation during run 2, while blue regions indicate higher activation during run 1.

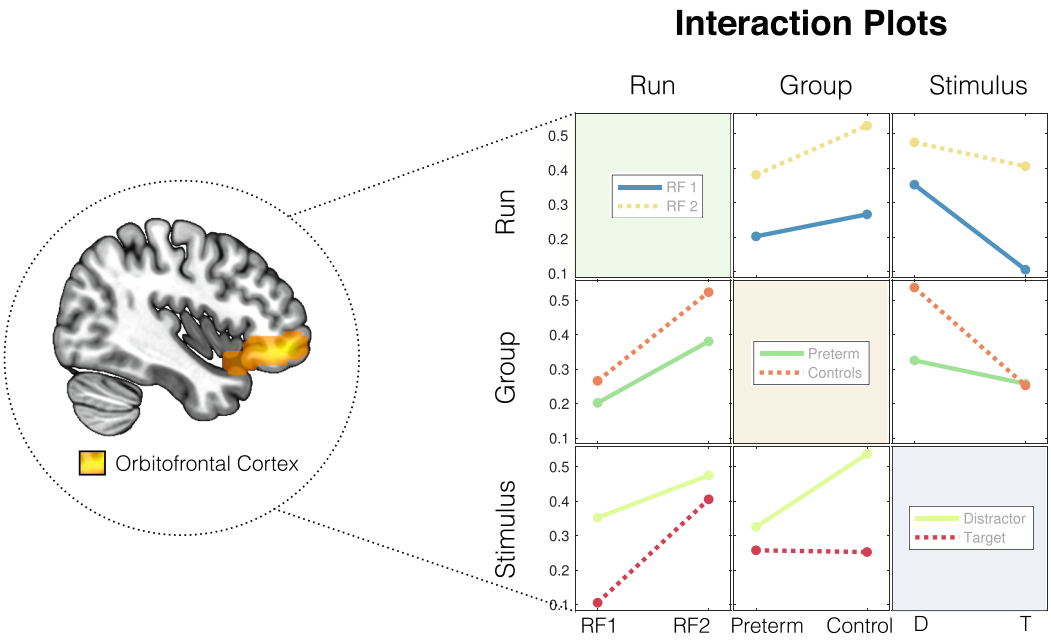

Fig. 5. Group, Run and Stimulus interaction effects in activation of the orbitofrontal cortex as a region of interest. Left: The orbitofrontal cortex (sagittal plane with MNI coordinate x = 40). Right: Interaction plots involving runs, groups and stimulus types. The y-axis of all plots represent the average BOLD signal for the corresponding factor (*e.g.*, run, group or stimulus).

4.2. Comparison of whole-brain activation during the two task runs

During performance of the first run of the experiment the activation of the posterior parietal cortex was higher compared to the second run. The first run of the task demands to recognize if an image has been already seen or not, and the posterior parietal cortex is implicated in recognition memory (Haramati et al., 2008), working memory and memory recollection (Sestrieri et al., 2017). In addition, this region is one of the nodes of the default mode network, which is typically activated during internally-oriented attention. Given that the same set of images is used for both runs, run 2 is significantly harder than run 1. This is because, in run 2, subjects must not only recognise images that were already seen during the current run, but also suppress memories from the previous one. The fact that the activation of these areas is higher during the first run is thus in line with previous studies which found that default mode network activation is inversely proportional to task demand (Čeko et al., 2015). This finding may be interpreted as a greater occurrence of moments of introspection or mind-wandering during run 1 given the ease of the task.

Studies in healthy adults using a more difficult version of the task showed that the first run is associated to the hippocampal area activation. The fact that we did not find this activation using an easier version of the task could suggest that it was not enough challenging for our participants, as can be seen by the presence of a ceiling effect in both groups.

Run 2, in turn, requires more effort since participants must not only recognise images that have already been seen during the current run, but also filter the memory of those images that have only been already seen during the first run. It is thus not surprising that brain regions related to attentional control and information manipulation during working memory-related tasks such as the superior parietal lobule (Koenigs et al., 2009; Wu et al., 2016) are more highly activated during this run. In addition, the bilateral amygdala activation in the second run — which starts approximately 5 min after run 1 is completed — is likely due to this region's role in memory consolidation (Roozendaal and McGaugh, 2011), a process that usually takes 5–10 min (Dharani, 2015). The implication of amygdala during the second run of the task could also suggest that this region is needed for orbitofrontal reality filtering. Indeed, amygdala is part of the lateral limbic loop, connecting amygdala to dorsomedial thalamus and OFC. This loop is probably the neuroanatomical substrate of ORFi (Schnider, 2018). Since OFC is one of the last cerebral regions to develop, we could hypothesize that this structure is more activated in children compared to adults during task's completion, and that its activation is not needed anymore once OFC is fully operational.

On the basis of adult literature, an higher activation of OFC in the second run was expected, since it is in this part of the task that orbitofrontal reality filtering is required. There are two possible explanations for the lack of activation of this specific region. Firstly, it is important to note that in this analysis we averaged together the activation for both Targets and Distractors. The OFC activation is known to be mainly needed in response to Distractors of run 2, when participants have to reject an image that has already been seen in the previous run, but not in the ongoing one. Therefore, we may have decreased the statistical power to find this specific region by pooling together Targets and Distractors in each run. In addition, results from Sections 3.4 and 3.5 clearly indicates that the processing of ORFi activated OFC in the control group but not in the preterm group. In this first part of the analysis, we pooled together participants from both groups. Therefore, it is possible that the specific OFC activation expected in run 2 may have been averaged out since preterm adolescents evoked different brain regions to perform the task.

4.3. Group comparison of whole-brain activation during the two task runs

We found significant differences in activation during the performance of the reality filtering task when comparing the two groups. We identified increased activation of the orbitofrontal cortex in term-born young adolescents as compared to their preterm-born peers. By itself, this result could have been achieved under three scenarios: 1) high activation of the OFC in the control group during task performance; 2) de-activation of the OFC in the preterm group; 3) or a combination of the two. The *post hoc* analysis of the individual groups indicated that the first hypothesis is true: this difference is due to high activation of the OFC in the term-born participants. The high activation of OFC in the control

group is in line with previous investigations that identify the OFC as a mediator of Reality Filtering in healthy populations (Schnider et al., 2000; Treyer et al., 2003; Schnider, 2018), including previous work on healthy young adolescents (Liverani et al., 2020). Failure to process reality filtering functions has been a consistent marker of reality confusion in clinical patients with damage in the OFC or in structures directly connected to it (Schnider and Ptak, 1999; Nahum et al., 2012). The fact that the preterm individuals did not activate the OFC as highly may be linked to previous findings of delayed development of frontal areas in this population (Nosarti et al., 2014; Sripada et al., 2018). However, that they are still able to perform the task despite lower activation in the OFC can mean one of two things: either they have developed a more efficient way of performing the same task that requires less use of this region, or the lack of development of this area has been compensated by other processes. This is further discussed in the next subsection.

Regions related to visual attention were also more active in the preterm than in the control group. This was surprising in a way, since nodes of the attention network have been consistently found to be less active in the preterm population (Olsen et al., 2018). Our inspection of the contrast values for individual groups revealed that this was due to decreased activation of attention-related areas in the control group. This is probably due to the fact that the task was too easy, not only for this age group in general, but more so for the controls than the preterm-born participants. Moreover, the comparatively lower activation of the OFC, combined with more activation of visual attention areas, suggests that in the preterm group the performance of this task requires the recruitment of more brain regions as compared to controls. This is in line with reported findings of increased functional segregation in this population (Cao et al., 2016; Sa de Almeida et al., 2021).

Preterm young adolescents also had significantly higher activation in motor areas related to finger movement than their term-born counterparts. This difference was due to an increase in activation in these areas in the preterm group, rather than de-activation in the control group. While this may seem unexpected, given that all participants performed both runs of the task by clicking mouse buttons with the right hand fingers, it is in line with previous research (Heep et al., 2009; Arichi et al., 2010; Allievi et al., 2016). Heep et al. (2009) and Arichi et al. (2010) found in separate studies that unilateral motor stimulation led to bilateral activation of the sensorimotor cortex in preterm infants, and it is a common clinical observation that they tend to have more associated hand movements than term-born peers.

4.4. Interactions between whole-brain group and run effects

Although the two runs of our experiment have the same instruction (*i.e.*, to identify images that were repeated during the current run), it is during the second run that orbitofrontal reality filtering is required. This is because during run 2, while recognising images as already seen, participants must also decide whether those have been already seen during the current run or only the previous one. Thus, investigating interactions between group and run effects was important for us to further understand what aspects of reality filtering were really different between groups. Although the results from this analysis did not survive multiple comparison correction, they point towards a few interesting trends. For instance, the dorsolateral prefrontal cortex and posterior parietal cortices were more highly activated in the control group during run 2. These regions are key nodes of the frontoparietal network, which is crucial for the ability to coordinate behaviour in a flexible, accurate and timely manner (Marek and Dosenbach, 2018). In addition, the control group showed higher increase in orbitofrontal cortex activation during the second run than the preterm-born individuals. This is in line with previous research showing that preterm birth is linked to altered development of frontal structure, function and connectivity (Sripada et al., 2018). Interestingly, however, young adolescents born preterm were able to perform the task successfully with a low rate of errors. This may be due to different hypotheses. Firstly, there may be a compensatory mechanism involving other parts of the brain that allow the preterm group to perform the task through different routes. However, no brain areas were significantly more active in this population than in the control group during the second run. Moreover, since there was a ceiling effect in the accuracy of the responses from both groups, this could be due to the task having been too easy for this age. Our results indicate that both options could be potential explanations. However, as discussed in Section 4.6 (Challenges and Limitations), further studies involving a more difficult version of the task would help clarify this issue.

4.5. Group, Run and Stimulus interaction effects on OFC activation

Given the known role of the OFC in mediating reality filtering processing, we performed additional analyses using this area as a region of interest. Although the results were not statistically significant (and we discuss the possible reasons in Section 4.6), the trends we found were extremely interesting, and we chose to report them to serve as a base for future studies. For instance, while the fact that OFC activation was higher in both groups during performance of run 2, and higher in the term-born group than in the preterm-born group during both runs agrees with our whole-brain results, this analysis illustrates that the difference in activation between the two runs was larger in the control group.

BOLD signal in the OFC was stronger in general during the second run independently of the type of stimulus, and the increase in activation was higher for stimuli of the Distractor type rather than of the Target type. This is in line with previous research indicating that the role of the OFC in reality filtering relates to suppressing memories that are not currently relevant (thus while processing images of the Distractor type during run 2, Schnider, 2018). Further, the control group shows a larger increase in activation during presentation of Distractor stimuli from moments when Target stimuli where presented, as compared to their preterm peers. Since the young adolescents that were born preterm were able to perform the task with high accuracy, this suggests that this group have found an optimal way to process this function that do not completely rely specifically on OFC, as tipically developing adolescents and adults do. Therefore, they probably use a larger panel of brain regions, which is in line with the higher functional segregation of this population. In addition, this suggests that OFC could have a minor functional specificity in the preterm population, because of the detrimental impact of early birth on the development of this vulnerable region.

4.6. Challenges and future directions

As described before, both groups performed the task very well, such that nearly no mistakes were ever made, preventing us from being able to investigate potential correlations between brain activation and accuracy levels. It is thus possible that we have missed higher activation of regions involved in the processing of this task. Future studies involving young adolescents should thus increase the difficulty of the task by methods such as increasing the number of trials, shortening the time for individual trials, and/ or adding different types of distractor elements (*e.g.*, images never repeated during run 1 that reappear during run 2, and images that appear for the first time in run 2). By increasing the difficulty of the task in these ways, regions that activate specifically for the reality filtering task may become more evident due to an increased effect. In addition, this will allow us to investigate differences in functional processing of accurately (versus incorrectly) recognised trials.

Crucially, although there is room for improvement, this study already sheds important light into differences between reality filtering processing in individuals born preterm or at term, and presents compelling avenues for future research.

5. Conclusion

In this study, we investigated the neurological underpinnings of a reality filtering task performance in young adolescents born prematurely as compared to their term-born peers. We identified differences in activation in the two groups while performing the two steps of the task and framed them within previous knowledge on preterm birth and reality filtering processing. Our results corroborate the idea that compensatory mechanisms are in place to make up for preterm birth-related difficulties, allowing individuals to perform functional tasks. Such results may be used as biomarkers for future studies on potential interventions to help this population.

CRediT authorship contribution statement

Lorena G.A. Freitas: Methodology, Software, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Maria Chiara Liverani:** Conceptualization, Formal analysis, Investigation, Writing - original draft, Writing - review & editing, Project administration. **Vanessa Siffredi:** Investigation, Writing - review & editing, Project administration. **Armin Schnider:** Conceptualization, Methodology, Writing - review & editing. **Cristina Borradori Tolsa:** Writing - review & editing. **Russia Ha-Vinh Leuchter:** Writing - review & editing, Supervision. **Dimitri Van De Ville:** Methodology, Supervision. **Petra S. Hüppi:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Funding acquisition.

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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