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A B S T R A C T

Objective: To assess the association between estimated whole-brain and lobe-specific radiofrequency electromagnetic fields (RF-EMF) doses, using an improved integrated RF-EMF exposure model, and brain volumes in preadolescents at 9–12 years old.

Methods: Cross-sectional analysis in preadolescents aged 9–12 years from the Generation R Study, a population-based birth cohort set up in Rotterdam, The Netherlands (n = 2592). An integrated exposure model was used to estimate whole-brain and lobe-specific RF-EMF doses (mJ/kg/day) from different RF-EMF sources including mobile and Digital Enhanced Cordless Telecommunications (DECT) phone calls, other mobile phone uses than calling, tablet use, laptop use, and far-field sources. Whole-brain and lobe-specific RF-EMF doses were estimated for all RF-EMF sources together (i.e. overall) and for three groups of RF-EMF sources that lead to a different pattern of RF-EMF exposure. Information on brain volumes was extracted from magnetic resonance imaging scans.

Results: Estimated overall whole-brain RF-EMF dose was 84.3 mJ/kg/day. The highest overall lobe-specific dose was estimated in the temporal lobe (307.1 mJ/kg/day). Whole-brain and lobe-specific RF-EMF doses from all RF-EMF sources together, from mobile and DECT phone calls, and from far-field sources were not associated with global, cortical, or subcortical brain volumes. However, a higher whole-brain RF-EMF dose from mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet was associated with a smaller caudate volume.

Conclusions: Our results suggest that estimated whole-brain and lobe-specific RF-EMF doses were not related to brain volumes in preadolescents at 9–12 years old. Screen activities with mobile communication devices while

Abbreviations: RF-EMF, radiofrequency electromagnetic fields; MRI, magnetic resonance imaging; DECT, Digital Enhanced Cordless Telecommunications; mJ, millijoule; min, minutes; W, watt; IQR, interquartile range; IQ, intelligence quotient; BMI, body mass index; B, beta; CI, confidence interval

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wirelessly connected to the internet lead to low RF-EMF dose to the brain and our observed association may thus rather reflect effects of social or individual factors related to these specific uses of mobile communication devices. However, we cannot discard residual confounding, chance finding, or reverse causality. Further studies on mobile communication devices and their potential negative associations with brain development are warranted, regardless whether associations are due to RF-EMF exposure or to other factors related to their use.

1. Introduction

Children have dramatically increased their use of mobile communication devices such as mobile phones or tablets in the last decade (Birks et al., 2018; ICT, 2017). The use of these devices has raised concerns among paediatricians, parents, teachers, and public health practitioners due to their possible negative health consequences (Vijayalaxmi and Scarfi, 2014; SSM's council, 2016). One of the concerns is related to the exposure to radiofrequency electromagnetic fields (RF-EMF) emitted by these devices (Foerster et al., 2018; Roser et al., 2017; World Health Organization, 2014). Children are the most vulnerable part of the population to the potential RF-EMF effects as their brain is still rapidly developing (Kheifets et al., 2005). Moreover, children will experience long periods of exposure to RF-EMF because they start using mobile communication devices at an early age and are likely to continue using them through their life.

Brain development is a multistep process beginning early in gestation and continuing into the postnatal period (Rice and Barone, 2000). Brain magnetic resonance imaging (MRI) has been used to examine typical and atypical morphological brain development and some associations have been described between brain volume alterations and cognitive function and behavioural problems (Arhan et al., 2017; Blanken et al., 2015; Libero et al., 2014; Pangelinan et al., 2011). However, epidemiological studies examining the association between RF-EMF exposure and brain development in children have only used neuropsychological tests or questionnaires measuring cognitive function and behavioural problems (Guxens et al., 2016, 2018; Redmayne et al., 2016; Roser et al., 2016; Schoeni et al., 2015a, 2015b; Thomas et al., 2010; Zheng et al., 2014). The study of brain volumes using MRI might give insight to the potential structural brain alterations behind some of the observed associations between RF-EMF exposure and cognitive function and behavioural problems.

Another important issue in this type of research is the assessment of the exposure to RF-EMF. Most epidemiological studies have used parental or self-reported information on use of different mobile communication devices (e.g. mobile phone, Digital Enhanced Cordless Telecommunications (DECT) phone, tablet) (Abramson et al., 2009; Bhatt et al., 2017; Guxens et al., 2016; Redmayne et al., 2016; Schoeni et al., 2015; Thomas et al., 2010; Zheng et al., 2014), estimated residential exposure to RF-EMF from mobile phone base stations (Guxens et al., 2016), or measured personal exposure of different RF-EMF sources using portable devices for a short period of time (Heinrich et al., 2010). All these approaches only assessed a portion of the overall RF-EMF exposure. Thus an estimation that would integrate the exposure of all RF-EMF sources, and more specifically that would also estimate the dose of RF-EMF received in the brain, is needed to better investigate the potential associations between RF-EMF exposure and brain development. So far, only one study developed an RF-EMF exposure model which included several RF-EMF exposure sources and estimated the RF-EMF dose of all these sources received in the whole brain (Roser et al., 2015). They found that higher estimated whole-brain RF-EMF dose was not associated with behavioural problems and concentration capacity but was related to lower figural memory in children and adolescents at 12–17 years old (Foerster et al., 2018; Schoeni et al., 2015; Roser et al., 2016). In the present study, we use a recently developed integrated RF-EMF exposure model including a larger number of RF-EMF exposure sources and the assessment of lobe-specific RF-EMF doses, which allows for a more comprehensive study of the potential association between RF-EMF exposure and brain development. Moreover, we estimated whole-brain and lobe-specific RF-EMF doses from three groups of RF-EMF sources that lead to a different pattern of RF-EMF exposure: i) brain RF-EMF doses from mobile and DECT phone calls which are the primary contributors of RF-EMF exposure to the brain leading to peak exposures very close to the head but for short periods of time; ii) brain RF-EMF doses from mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet which lead to low doses and might mainly represent a variety of social or individual factors related to these type of uses; and iii) brain RF-EMF doses from far-field sources (e.g. mobile phone base stations, FM radio and TV broadcast antennas, WiFi) which lead to low doses but are received continuously along the day (Birks et al., 2018; Birks et al., 2020).

Therefore, the aim of the current study was to assess the association between estimated whole-brain and lobe-specific RF-EMF doses using an improved integrated RF-EMF exposure model and brain volumes in preadolescents at 9–12 years old.

2. Methods

2.1. Study design and population

This is a cross-sectional analysis embedded in the Generation R Study, a population-based birth cohort study from fetal life onwards in Rotterdam, the Netherlands. A total of 9901 pregnant women were enrolled and children were born between April 2002 and January 2006. Between 2013 and 2015, a total of 3992 preadolescents at 9–12 years old underwent a MRI assessment, and 3303 of them had information on mobile communication devices use. After excluding preadolescents with incidental findings or poor neuroimaging quality, we included 2592 preadolescents (26.2% of the original cohort) in our analyses (Supplementary Fig. S1). The Medical Ethics Committee of the Erasmus Medical Centre approved the study and written informed consent was obtained from parents.

2.2. Estimated whole-brain and lobe-specific RF-EMF dose

We applied an integrative RF-EMF exposure model to estimate whole-brain and lobe-specific (i.e. frontal, parietal, temporal, occipital) RF-EMF doses due to several RF-EMF exposure sources (Birks et al., 2020; Liorni et al., 2020; van Wel et al., 2020). This model is built using information on the use of mobile communication devices (i.e. near-field RF-EMF sources) and estimations of exposure to environmental RF-EMF sources (i.e. far-field RF-EMF sources).

2.2.1. Near-field RF-EMF sources

Information of the use of mobile communication devices close to the body was reported by one of the parents using questionnaires when participants were 9–12 years. Duration of use of (i) mobile phone for calling, (ii) DECT phone for calling, (iii) mobile phone for internet browsing, e-mailing, and text messaging while wirelessly connected to the internet (named other mobile phone uses), (iv) tablet while wirelessly connected to the internet, and (v) laptop while wirelessly connected to the internet were collected in minutes/day.

2.2.2. Far-field RF-EMF sources

We estimated RF-EMF exposure to different environmental RF-EMF sources (mobile phone base stations, FM radio and TV broadcast antennas, mobile phones, DECT phones, and WiFi) based on the microenvironments where preadolescents spend most of their time such as home, school, commuting, and outdoors.

To estimate RF-EMF exposure from mobile phone base stations at home, a validated 3D geospatial radio wave propagation model called NISMap was used (Beekhuizen et al., 2013, 2014; Bürgi et al., 2009; Huss et al., 2015). In brief, NISMap computes the field strengths induced by emissions from mobile phone base stations for any location in 3D-space using detailed characteristics of the antennas and the 3D geometry of the urban environment. The model has been validated with outside, inside, and personal measurements showing reliable rank-order predictions (Beekhuizen et al., 2013, 2014; Martens et al., 2015). We assessed the emission in three mobile phone communication bands that were in use at the time of the study (GSM900, GSM1800, and UMTS) using a country-wide mobile phone base stations data set from 2014. Using the geo-coded address of each child and the floor level of his/her bedroom at the time of the brain imaging, we computed the RF-EMF exposure from mobile phone base stations at each preadolescent's bedroom.

RF-EMF exposure from mobile phone base stations in the other microenvironments besides home and from the other far-field RF-EMF sources (FM radio and TV broadcast antennas, mobile phones, DECT phones, and WiFi) in all microenvironments was approximated using the average of personal RF-EMF measurements of up to 72 hours by 56 preadolescents of around 12 years of age in Amsterdam in a previous study (Birks et al., 2018), as data was not available for the participants of the Generation R Study.

2.2.3. Integrated RF-EMF exposure model

We applied the integrated RF-EMF exposure model to estimate whole-brain and lobe-specific (i.e. frontal, parietal, temporal, occipital) RF-EMF doses (Birks et al., 2020; Liorni et al., 2020; van Wel et al., 2020). Briefly, the model combines three types of information: i) the estimated ratio of the absorbed power to the mass in which it is absorbed of each specific RF-EMF source for each brain region which already takes into account the protection role of the head, known as specific absorption rate (SAR, in Watts (W)/kilogram (kg)), normalized to 1 W output power, ii) the output power of each RF-EMF source and activity (in W), and iii) the daily duration of use or exposure of each RF-EMF source and activity (in minutes (min)/day). First, for each brain region the model estimated a specific RF-EMF dose (millijoules (mJ)/kg/day) to each RF-EMF source (mobile phone calls, DECT phone calls, other mobile phone uses, tablet use, laptop use, and far-field) as follows:

$$\textbf{Specific RF-EMF dose}_{\text{brain region, source}} = \textbf{SAR}_{\text{brain region, source}} \times \textbf{Output power}_{\text{source}} \times \textbf{Duration}_{\text{source}} \tag{1}$$

Then, overall whole-brain RF-EMF doses and overall frontal, parietal, temporal, and occipital RF-EMF doses were calculated combining the specific RF-EMF doses of all RF-EMF sources by brain region:

$$\textbf{Overall RF-EMF dose}_{\text{brain region}} = \sum\nolimits_{\text{source}} (\textbf{SAR}_{\text{brain region, source}} \times \textbf{Output power}_{\text{source}} \times \textbf{Duration}_{\text{source}}) \tag{2}$$

Moreover, whole-brain and lobe-specific RF-EMF doses for three groups of RF-EMF exposure sources ((i) mobile and DECT phone calls (named phone calls), (ii) other mobile phone uses, tablet use, and laptop use while wirelessly connected to the internet (named screen activities), and (iii) far-field sources) were calculated following the same procedure.

To apply the integrated RF-EMF exposure model, we had to make some assumptions (van Wel et al., 2020). Based on the mobile phone use in preadolescents, adolescents, and young adults in Europe collected in the same period of time than in our study, we assumed a proportion of 35% 2G calls, 65% 3G calls, and no hands-free devices use (Langer et al., 2017). Other mobile phone uses, laptop use, and tablet use were assumed to occur using WiFi at 2.4 GHz and WiFi data transfer rates were estimated to be 54 Megabits per second. During the timeslots where preadolescents were using other mobile phone uses, we assumed that preadolescents were 40% of that time playing video games, 40% of that time streaming video, and 20% of that time browsing the internet or checking social media. For each device and activity, we averaged the SAR values from the different possible positions of use available to obtain one SAR value per activity that could be inserted in Equation (1) and (2).

2.3. Brain volumes

To familiarize the participating preadolescents with magnetic resonance environment, each preadolescent underwent a mock scanning session prior to the actual MRI session (White et al., 2018). The scans were performed on a 3 Tesla General Electric scanner (GE, MR750W, Milwaukee, USA) using an 8-channel receive-only head coil. The structural T1 images were obtained using the following sequence parameters: TR = 8.77 ms; TE = 3.4 ms; TI = 600 ms; Flip Angle = 10°; FOV = 220 mm × 220 mm; acquisition matrix = 220 × 220; slice thickness = 1 mm; number of slices = 230; voxel size = 1 mm × 1 mm × 1 mm; and ARC Acceleration = 2. The obtained T1 images were then processed through the FreeSurfer analysis suite, version 6.0 (Fischl, 2012). Global metrics of cortical and subcortical volumes were extracted. For our analysis we included the volumes of the total brain, cortical gray matter, cortical white matter, cerebellar gray matter, and cerebellar white matter as global brain volumes. The volumes of frontal, parietal, temporal, and occipital lobes were included as cortical lobar volumes. The volumes of the hippocampus, amygdala, thalamus, putamen, caudate, nucleus accumbens, and pallidum were considered as subcortical volumes (Supplementary Table S1). The pre-processing, correction, and assessment of the quality of the images are described in detail elsewhere (Muetzel et al., 2018).

2.4. Potential confounding variables

The potential confounding variables were *a priori* defined with a Directed Acyclic Graph (Hernán et al., 2002). Maternal and family characteristics included maternal ethnicity (Dutch, Asian, African, or European and others) collected during pregnancy, maternal educational level (primary or lower (low), secondary (medium), or university or higher (high)) collected when the child was 5 years old, as well as maternal smoking (yes vs. no), employment status (paid vs. non-paid), household income (< 2000€/month (low), 2000–3999€ (medium), or > 3999€ (high)) and anxiety and depressive symptoms assessed using the Brief Symptom Inventory (de Beurs and Zitman, 2006; L.R. Derogatis and N. Melisaratos, 1983) collected when the child was 9–12 years old. Preadolescent's characteristics included age at the brain imaging assessment, sex collected at birth, intelligence quotient assessed using the Snijders-Oomen Nonverbal Intelligence test (Tellegen et al., 1998) at 5 years old, and body mass index (kg/m^2) measured at 9–12 years old.

2.5. Other covariates

We also collected information on preadolescent's handedness due to the previously reported differences in brain volumes between right and left-handers (Jang et al., 2017).

2.6. Statistical analysis

After checking that all assumptions of the models were fulfilled, we used linear regression models to assess the association between overall and source-specific whole-brain RF-EMF doses and global and subcortical brain volumes, and between overall and source-specific RF-EMF doses to each specific lobe and cortical lobar volumes. We also adjusted our models for the potential confounding variables described above and preadolescent's handedness. All models were corrected for multiple testing using false discovery rate (Simes, 1986). We applied false discovery rating at once to a total of 64 tests and we obtained corrected critical p-values for each association. Additionally, we adjusted cortical lobar volumes, subcortical volumes, and cortical gray matter, cortical white matter, cerebellar cortex, and cerebellar white matter volumes for intracranial volume to ascertain relativity to the head size. Total brain volume was not adjusted for intracranial volume because they were highly correlated ($r = 0.93$).

Multiple imputation of missing confounding variables was performed using chained equations where 25 completed datasets were generated and analyzed (Nguyen et al., 2017). The percentage of missing values was < 18% and distributions in imputed datasets were very similar to those in the observed dataset (data not shown). Preadolescents included in the analysis (n = 2592) were more likely to have parents with a higher level of education, with a higher household income, and older compared with those non-included (n = 7309) (Supplementary Table S2). We used inverse probability weighting to correct for loss to follow-up and account for potential selection bias when including only preadolescents with available data (n = 2592) compared to the full cohort recruited at pregnancy (n = 9901).

All analyses were performed using Stata version 15 (StataCorp, College Station, TX).

3. Results

Most of the preadolescents had Dutch and highly educated mothers and were from middle or high income families (Table 1). Estimated overall whole-brain RF-EMF dose was 84.3 mJ/kg/day and the highest dose was estimated in the temporal lobe (307.1 mJ/kg/day). The major contributor to the overall whole-brain RF-EMF dose was the dose from mobile and DECT phone calls (61.5%) while the dose from screen activities with mobile communication devices while wirelessly connected to the internet and from far-field sources contributed 17.4% and 21.1%, respectively (Supplementary Table S3). These percentages varied between each lobe-specific RF-EMF dose. Overall whole-brain RF-EMF dose was highly correlated with overall lobe-specific RF-EMF doses ($r > 0.79$) and source-specific whole-brain RF-EMF doses were not correlated between each other (between −0.02 and −0.12) (data not shown). The associations between maternal, family, preadolescents' characteristics and overall and source-specific estimated whole-brain RF-EMF doses are shown in Table S4.

None of the estimated whole-brain RF-EMF doses was associated with global brain volumes (Table 2). Regarding cortical lobar volumes, only higher estimated frontal RF-EMF dose from screen activities with mobile communication devices while wirelessly connected to the internet was related to a smaller frontal lobe volume [B − 39.72 mm^3 (95% CI −78.23; −1.21)] (Table 3). However, this association did not remain after correcting for multiple testing. Overall estimated whole-brain RF-EMF dose and whole-brain RF-EMF dose from mobile and DECT phone calls and from far-field sources were not related to subcortical volumes (Table 4). However, higher estimated whole-brain RF-EMF dose from screen activities with mobile communication devices while wirelessly connected to the internet was associated with smaller caudate volume [B −5.02 mm^3 (95% CI −7.78; −2.25)] and this association remained after correcting for multiple testing. Associations did not materially change after adjusting for intracranial volume (data not shown).

4. Discussion

In the present study, we applied an improved integrated RF-EMF exposure model to estimate whole-brain and lobe-specific RF-EMF doses including several RF-EMF exposure sources and we investigated their association with brain volumes in preadolescents at 9–12 years of age. We did not find a relationship of estimated whole-brain or lobe-specific RF-EMF doses from overall RF-EMF sources, from mobile and DECT phone calls, or from far-field sources with global, cortical, or subcortical brain volumes. However, we found an association between higher estimated whole-brain RF-EMF dose from mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet, a group of RF-EMF sources that lead to low RF-EMF exposure to the brain, and smaller caudate volume.

We conducted the first epidemiological study exploring the relationship of RF-EMF brain doses with brain volumes in preadolescents. Most of the previous studies have assessed the association between the different RF-EMF sources separately and the development of the brain, but our integrative approach allows a more comprehensive assessment of the overall brain dose from several RF-EMF sources, as well as the brain dose from three groups of RF-EMF sources that lead to a different pattern of RF-EMF exposure. We did not find an association between estimated whole-brain or lobe-specific RF-EMF doses from overall RF-EMF sources or from mobile and DECT phone calls and brain volumes.

Table 1
Distribution of maternal, family, and preadolescent characteristics, and overall whole-brain and lobe-specific RF-EMF doses (n = 2592).

	Distribution
Maternal characteristics	
Ethnicity, %	
Dutch	60.9
Asian	19.6
African	10.1
European and others	9.4
Educational level, %	
High	54.9
Medium	39.2
Low	5.9
Smoking (yes vs. no), %	13.5
Depressive symptoms[a], median (IQR)	0.0 (0.0; 0.2)
Anxiety symptoms[a], median (IQR)	0.2 (0.0; 0.3)
Employment status (paid vs. non-paid), %	79.4
Family characteristics	
Household income, %	
High	42.3
Medium	39.2
Low	18.5
Preadolescent characteristics	
Sex (female vs. male), %	50.7
Age (in years), median (IQR)	9.9 (9.8; 10.3)
IQ score at 5 years old[b], median (IQR)	103.0 (93.0; 113.0)
BMI at 9–12 years old (kg/m^2), median (IQR)	16.9 (15.7; 18.6)
Overall RF-EMF doses	
Whole-brain (mJ/kg/day), median (IQR)	84.3 (43.4; 155.5)
Frontal lobe (mJ/kg/day), median (IQR)	111.8 (66.5; 202.0)
Parietal lobe (mJ/kg/day), median (IQR)	81.6 (57.6; 147.0)
Temporal lobe (mJ/kg/day), median (IQR)	307.1 (70.8;612.8)
Occipital lobe (mJ/kg/day), median (IQR)	100.6 (62.3; 179.9)

BMI, body mass index; IQ, intelligence quotient; IQR, interquartile range; mJ, milijoules; kg, kilograms; RF-EMF, Radiofrequency Electromagnetic Fields.
If there are two categories: the listed percentage indicates the fraction in the first category.
[a] Higher score indicates more symptoms.
[b] Higher score indicates higher IQ.

Table 2
Association between estimated overall and source-specific whole-brain RF-EMF doses and global brain volumes (mm^3) in preadolescents at 9–12 years of age.

Whole-brain RF-EMF doses (Δ1 mJ/kg/day)	**Total brain B (95% CI)**	**Cortical gray matter B (95% CI)**	**Cortical white matter B (95% CI)**	**Cerebellar cortex B (95% CI)**	**Cerebellar white matter B (95% CI)**
Overall dose	−1.29 (−9.91; 7.32)	−0.97 (−5.24; 3.31)	−0.79 (−4.74; 3.16)	0.26 (−0.66; 1.18)	0.20 (−0.05; 0.44)
Specific doses					
Phone calls	−0.69 (−9.41; 8.03)	−0.68 (−5.01; 3.64)	−0.54 (−4.53; 3.46)	0.30 (−0.63; 1.23)	0.22 (−0.03; 0.47)
Screen activities[a]	−173.66 (−443.86; 96.53)	−60.22 (−194.31; 73.86)	−91.49 (−215.31; 32.33)	−12.20 (−41.07; 16.67)	−2.13 (−9.82; 5.57)
Far-field sources[b]	−20.74 (−79.40; 37.92)	−11.05 (−40.18; 18.08)	−8.04 (−34.91; 18.83)	−0.78 (−7.04; 5.49)	−0.64 (−2.31; 1.02)

B, Beta coefficient; CI, confidence interval; DECT, Digital Enhanced Cordless Telecommunications; kg, kilograms; mJ, millijoules; RF-EMF, Radiofrequency Electromagnetic Fields.
Linear regression models adjusted for maternal educational level, maternal ethnicity, maternal employment status, maternal smoking, maternal depressive and anxiety symptoms, household income, and child intelligence quotient, sex, age, body mass index, and handedness.
[a] Screen activities includes mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet.
[b] RF-EMF exposure from different environmental RF-EMF sources (mobile phone base stations, FM radio and TV broadcast antennas, mobile phones, DECT phones, and WiFi) from different microenvironments (home, school, commuting, and outdoors).

However, higher estimated whole-brain RF-EMF dose from other mobile phone uses, tablet use, and laptop use while wirelessly connected to the internet was associated with a smaller caudate volume. If this observed association was driven by the RF-EMF dose that the brain absorbs from the use of the mobile communication devices, we would expect to also find an association with the brain dose received from mobile and DECT phone calls. These are the primary contributors of RF-EMF exposure to the brain leading to peak exposures very close to the head, while mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet lead to low RF-EMF exposure to the brain including the subcortical brain structures such as the caudate (Birks et al., 2020). Thus there is concern whether the possible health effects of these specific uses of mobile phone, tablet, and laptop are due to social or individual factors related to the time preadolescents spend with these devices or the specific activities that they undertake with these devices instead of their emitted RF-EMF exposure. In our study, almost all participants reported to use these mobile communication devices always wirelessly connected to the internet, thus the estimated RF-EMF brain dose from each device and the reported time spent with each device were highly correlated (between 0.75 and 0.99). Hence, we were unable to disentangle them. Moreover, we might miss relevant information related to the use of these mobile communication devices which is essential for properly studying its relationship with brain development (e.g. type of screen activity performed with these devices, family structure, psychological well-being, or relationship with friends). Therefore, we cannot entirely discard that our results are due to residual confounding or to chance finding. Moreover, reverse causality could also explain our results. Children and young adults with some psychiatric disorders such as Attention-Deficit/Hyperactivity Disorder have been shown to have a smaller caudate brain volume (Greven et al., 2015; Hoogman et al., 2017; Voelbel et al., 2006), and it could be hypothesized that individuals with these disorders have a higher use of mobile communication devices. Given that the potential relationship of RF-EMF exposure and brain volumes was not investigated to date, our analysis was exploratory and needs to be replicated in other population-based studies. Moreover, further studies are warranted due to the expected increase in the use of mobile communication devices and changes in RF-EMF exposure (e.g. introduction of new devices to the market, changes in the patterns of use such as more texting and less calling, or changes in network and devices characteristics such as the introduction of the 5G technology).

Experimental studies in animals have previously showed that exposure to RF-EMF is related to brain morphology alterations. In particular, higher RF-EMF exposure induced denditric remodelling and decreased viable cells in the hippocampus and the amygdala in rats

Table 3
Association between estimated overall and source-specific RF-EMF doses to each brain lobe and cortical lobar volumes (mm^3) in preadolescents at 9–12 years of age.

Lobe-specific RF-EMF doses (Δ1 mJ/kg/day)	**Frontal lobe B (95% CI)**	**Parietal lobe B (95% CI)**	**Temporal lobe B (95% CI)**	**Occipital lobe B (95% CI)**
Overall dose	−0.19 (−1.89; 1.51)	−1.43 (−3.84; 0.98)	0.01 (−0.18; 0.20)	−0.36 (−1.13; 0.42)
Specific doses				
Phone calls	−0.04 (−1.84; 1.77)	−2.16 (−6.18; 1.87)	0.01 (−0.18; 0.21)	0.01 (−0.91; 0.93)
Screen activities[a]	**−39.72 (−78.23; −1.21)**	−17.89 (−61.11; 25.32)	−29.37 (−94.41; 35.67)	−2.68 (−26.11; 20.75)
Far-field sources[b]	−0.80 (−5.96; 4.37)	−0.97 (−3.99; 2.05)	−0.83 (−4.36; 2.71)	−1.29 (−2.74; 0.16)

B, Beta coefficient; CI, confidence interval; DECT, Digital Enhanced Cordless Telecommunications; kg, kilograms; mJ, millijoules; RF-EMF, Radiofrequency Electromagnetic Fields.
Linear regression models adjusted for maternal educational level, maternal ethnicity, maternal employment status, maternal smoking, maternal depressive and anxiety symptoms, household income, and child intelligence quotient, sex, age, body mass index, and handedness. In bold, p-value < 0.05.
[a] Screen activities includes mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet.
[b] RF-EMF exposure from different environmental RF-EMF sources (mobile phone base stations, FM radio and TV broadcast antennas, mobile phones, DECT phones, and WiFi) from different microenvironments (home, school, commuting, and outdoors).

Table 4
Association between estimated overall and source-specific whole-brain RF-EMF doses and subcortical volumes (mm^3) in preadolescents at 9–12 years of age.

Whole-brain RF-EMF doses (Δ1 mJ/kg/day)	**Hippocampus B (95% CI)**	**Amygdala B (95% CI)**	**Thalamus B (95% CI)**	**Putamen B (95% CI)**	**Caudate B (95% CI)**	**Nucleus accumbens B (95% CI)**	**Pallidum B (95% CI)**
Overall dose	−0.02 (−0.08; 0.05)	0.00 (−0.04; 0.03)	0.01 (−0.10; 0.12)	0.03 (−0.06; 0.13)	−0.02 (−0.11; 0.07)	0.01 (−0.01; 0.03)	0.00 (−0.03; 0.04)
Specific doses							
Phone calls	−0.02 (−0.08; 0.05)	0.00 (−0.03; 0.03)	0.02 (−0.10; 0.13)	0.03 (−0.07; 0.13)	−0.01 (−0.10; 0.08)	0.01 (−0.01; 0.03)	0.00 (−0.03; 0.04)
Screen activities[a]Screen activities[a]	0.86 (−1.13; 2.85)	0.13 (−0.89; 1.15)	−1.34 (−4.91; 2.22)	−0.38 (−3.46; 2.70)	**−5.02 (−7.78; −2.25)***	−0.48 (−1.02; 0.06)	−0.93 (−2.07; 0.22)
Far-field sources[b]	−0.05 (−0.49; 0.38)	−0.12 (−0.34; 0.10)	−0.19 (−0.96; 0.58)	0.30 (−0.36; 0.97)	−0.29 (−0.89; 0.31)	0.05 (−0.07; 0.17)	0.05 (−0.20; 0.30)

B, Beta coefficient; CI, confidence interval; DECT, Digital Enhanced Cordless Telecommunications; kg, kilograms; mJ, millijoules; RF-EMF, Radiofrequency Electromagnetic Fields.
Linear regression models adjusted for maternal educational level, maternal ethnicity, maternal employment status, maternal smoking; maternal depressive and anxiety symptoms, household income, and child intelligence quotient, sex, age, body mass index, and handedness. In bold and *, associations that remained after correction for multiple testing (p-value < corrected critical p-value (0.0008)).
[a] Screen activities includes mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet.
[b] RF-EMF exposure from different environmental RF-EMF sources (mobile phone base stations, FM radio and TV broadcast antennas, mobile phones, DECT phones, and WiFi) from different microenvironments (home, school, commuting, and outdoors).

(Hussein et al., 2016; Li et al., 2012; Narayanan et al., 2010, 2015, 2018). In our study, we did not find an association between the brain RF-EMF doses and the volume of the hippocampus or the amygdala. Unfortunately, we could not estimate RF-EMF doses in these subcortical structures. Among other functions, the hippocampus plays an important role in the formation of new memories (Leszczynski, 2011) and the amygdala is involved in memory consolidation (McGaugh, 2004). Interestingly, a longitudinal epidemiological study found that a higher estimated whole-brain RF-EMF dose in preadolescents and adolescents with right-side preference for the phone calls was related to a decreased figural memory performance, which involves mainly the right hemisphere (Golby et al., 2001), and not to verbal memory performance, which involves mainly the left hemisphere, after one year of follow-up (Foerster et al., 2018). The authors suggested that the association between RF-EMF brain dose and memory might be driven by disturbed sleep (Foerster et al., 2018), as previous studies found alterations in the electroencephalogram (EEG) during sleep in participants exposed to RF-EMF (Loughran et al., 2012; Lustenberger et al., 2015; Regel et al., 2007; Schmid et al., 2012) and disturbed sleep have been related to poorer memory consolidation (Taveras et al., 2017) and disturbed subcortical structures such as hippocampus (Koyanagi et al., 2019; Sawangjit et al., 2018). The brain is dynamic and responds to many external inputs, including environmental exposures. This dynamism might not always translate to detectable structural brain alterations but to small brain activity changes that could explain the observed associations between RF-EMF exposure and impaired cognitive function in previous studies (Abramson et al., 2009; Bhatt et al., 2017; Calvente et al., 2016; Foerster et al., 2018; Guxens et al., 2016; Heinrich et al., 2010; Redmayne et al., 2016; Roser et al., 2016; Schoeni et al., 2015a, 2015b; Thomas, 2010; Zheng et al., 2014), as well as the observed brain effects in animal studies (Jang et al., 2017; Nguyen et al., 2017; Simes, 1986; Voelbel et al., 2006; Tellegen et al., 1998). Studies investigating the relationship between brain exposure to RF-EMF and functional magnetic resonance imaging measures would be of interest.

The strengths of this study are the collection of detailed information on the use of mobile communication devices in a large cohort of preadolescents, the estimation of whole-brain and lobe-specific RF-EMF doses including a large number of RF-EMF exposure sources, and the availability of brain structural imaging data for about 2500 participants. The main limitation of this study is its cross-sectional design. If an association between RF-EMF exposure to the brain and brain volumes exists, effects might appear after a longer cumulative exposure. Thus studies with longitudinal data on both the use of mobile communication devices and brain volumes are needed. Moreover, we used an innovative and comprehensive tool to estimate brain RF-EMF doses but it builds on several assumptions which could lead to non-differential misclassification of the exposure leading to a potential underestimation of the effect estimates (Liorni et al., 2020; van Wel et al., 2020). In addition, the use of mobile communication devices was reported by the parents and did not include its use at school which might underestimate the actual use. Objective measures such as applications installed in preadolescents' devices tracking their actual use, previously validated, could be used in new studies to improve accuracy of the measurement of the use of mobile communication devices. Finally, although we adjusted our models for several potential confounding variables we cannot discard residual confounding for unavailable variables such as paternal socioeconomic status.

5. Conclusion

Our results suggest that estimated whole-brain and lobe-specific RF-EMF doses were not related to brain volumes in preadolescents aged 9–12 years. Our findings might also indicate that social or individual factors related to certain uses of mobile communication devices such as mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet, instead of the RF-EMF exposure to the brain by these uses, could be related to a smaller caudate volume, although we cannot discard residual confounding, chance finding, or reverse causality. Further studies on mobile communication devices and their potential negative associations with brain development are warranted, regardless whether associations are due to RF-EMF exposure or to other factors related to their use.

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CRediT authorship contribution statement

Alba Cabré-Riera: Conceptualization, Formal analysis, Investigation, Writing - original draft, Visualization. **Hanan El Marroun:** Conceptualization, Supervision, Writing - review & editing. **Ryan Muetzel:** Methodology, Software, Writing - review & editing. **Luuk van Wel:** Methodology, Software, Writing - review & editing. **Ilaria Liorni:** Methodology, Software, Writing - review & editing. **Arno Thielens:** Methodology, Writing - review & editing. **Laura Ellen Birks:** Formal analysis, Writing - review & editing. **Livia Pierotti:** Formal analysis, Writing - review & editing. **Anke Huss:** Funding acquisition, Writing - review & editing. **Wout Joseph:** Methodology, Funding acquisition, Writing - review & editing. **Joe Wiart:** Methodology, Writing - review & editing. **Myles Capstick:** Methodology, Funding acquisition, Writing - review & editing. **Manon Hillegers:** Funding acquisition, Writing - review & editing. **Roel Vermeulen:** Methodology, Funding acquisition, Writing - review & editing. **Elisabeth Cardis:** Funding acquisition, Writing - review & editing. **Martine Vrijheid:** Funding acquisition, Writing - review & editing. **Tonya White:** Methodology, Funding acquisition, Writing - review & editing. **Martin Röösli:** Conceptualization, Funding acquisition, Writing - review & editing. **Henning Tiemeier:** Conceptualization, Funding acquisition, Writing - review & editing. **Mònica Guxens:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

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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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105808.

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