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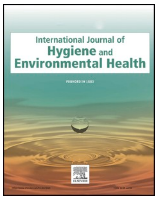

Association between estimated whole-brain radiofrequency electromagnetic fields dose and cognitive function in preadolescents and adolescents

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ABSTRACT

Objective: To investigate the association between estimated whole-brain radiofrequency electromagnetic fields (RF-EMF) dose, using an improved integrated RF-EMF exposure model, and cognitive function in preadolescents and adolescents.

Methods: Cross-sectional analysis in preadolescents aged 9–11 years and adolescents aged 17–18 years from the Dutch Amsterdam Born Children and their Development Study (n = 1664 preadolescents) and the Spanish INfancia y Medio Ambiente Project (n = 1288 preadolescents and n = 261 adolescents), two population-based birth cohort studies. Overall whole-brain RF-EMF doses (mJ/kg/day) were estimated for several RF-EMF sources together including mobile and Digital Enhanced Cordless Telecommunications phone calls (named phone calls), other mobile phone uses than calling, tablet use, laptop use (named screen activities), and far-field sources. We also estimated whole-brain RF-EMF doses in these three groups separately (i.e. phone calls, screen activities, and far-field) that lead to different patterns of RF-EMF exposure. We assessed non-verbal intelligence in the Dutch and Spanish preadolescents, information processing speed, attentional function, and cognitive flexibility in the Spanish preadolescents, and working memory and semantic fluency in the Spanish preadolescents and adolescents using validated neurocognitive tests.

Results: Estimated overall whole-brain RF-EMF dose was 90.1 mJ/kg/day (interquartile range (IQR) 42.7; 164.0) in the Dutch and Spanish preadolescents and 105.1 mJ/kg/day (IQR 51.0; 295.7) in the Spanish adolescents.

Abbreviations: RF-EMF, radiofrequency electromagnetic fields.

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Higher overall estimated whole-brain RF-EMF doses from all RF-EMF sources together and from phone calls were associated with lower non-verbal intelligence score in the Dutch and Spanish preadolescents (−0.10 points, 95% CI -0.19; −0.02 per 100 mJ/kg/day increase in each exposure). However, none of the whole-brain RF-EMF doses was related to any other cognitive function outcome in the Spanish preadolescents or adolescents.

Conclusions: Our results suggest that higher brain exposure to RF-EMF is related to lower non-verbal intelligence but not to other cognitive function outcomes. Given the cross-sectional nature of the study, the small effect sizes, and the unknown biological mechanisms, we cannot discard that our resultsare due to chance finding or reverse causality. Longitudinal studies on RF-EMF brain exposure and cognitive function are needed.

1. Introduction

Mobile communication devices such as phones and tablets emit electromagnetic fields (EMF) in the radiofrequency (RF) range of 3 kHz–300 GHz. Exposure to RF-EMF has become ubiquitous because of the enormous increase in the use of mobile communication devices in recent years, especially in late childhood (Birks et al., 2018; Crone and Konijn, 2018; IARC, 2013; ICT, 2017; Sage and Burgio, 2018; van Deventer et al., 2011). Adolescents might be more vulnerable to the potential RF-EMF health effects than adults, especially in their cognitive function, because their brain is still developing (Gerber et al., 2009; Kheifets, 2005; Rice and Barone, 2000).

Studies in mice and rats suggest that exposure to RF-EMF increases the permeability of the blood brain barrier, impairs intracellular calcium homeostasis, alters neurotransmitter regulation, and causes neuronal loss. These reports also show that RF-EMF damages brain tissues like the cerebral cortex (Kim et al., 2017). In addition, studies in humans show both positive and negative cognitive effects after or during exposure to RF-EMF (Barth et al., 2012; Valentini et al., 2010; Vecsei et al., 2018; Verrender et al., 2016). Thus currently evidence is not sufficient to draw any definite biological mechanism. Also, several epidemiological studies have investigated the association between RF-EMF exposure and cognitive function in 5 to 18-year-olds, showing mixed results (Abramson et al., 2009; Bhatt et al., 2017; Foerster et al., 2018; Guxens et al., 2016; Heinrich et al., 2010; Redmayne et al., 2016; Schoeni et al., 2015a, 2015b; Thomas et al., 2010; Zheng et al., 2014). Most of these studies assessed brain RF-EMF exposure only taking into consideration proxies of exposure such as maternal- or self-reported phone calls from mobile or Digital Enhanced Cordless Telecommunications (DECT) (Abramson et al., 2009; Bhatt et al., 2017; Guxens et al., 2016; Redmayne et al., 2016; Schoeni et al., 2015a, 2015b; Thomas et al., 2010; Zheng et al., 2014) and only one cohort study estimated the actual whole-brain dose received from some RF-EMF sources (Schoeni et al., 2015a; Roser et al., 2016; Foerster et al., 2018). This cohort study found that higher whole-brain RF-EMF dose was related to lower figural memory (Foerster et al., 2018; Schoeni et al., 2015a) but not to concentration capacity (Roser et al., 2016) in 12 to 17-year-olds. Patterns of mobile communication devices use are different between ages during adolescence (Eeftens et al., 2018). Therefore, a broader assessment of RF-EMF exposure to the brain by integrating all RF-EMF sources according to usage patterns will result in a more accurate and comprehensive dose estimation.

The aim of this study was to investigate the association between estimated overall and source-specific whole-brain RF-EMF dose and cognitive function in two brain development periods: preadolescence (9–11 years of age) and adolescence (17–18 years of age). We used a recently developed method to estimate whole-brain RF-EMF dose with the advantage of integrating a large number of RF-EMF sources resulting in a more accurate and comprehensive estimation.

2. Methods

2.1. Study design and population

This cross-sectional analysis used data from two population-based birth cohort studies, the Dutch Amsterdam Born Children and their Development (ABCD) Study (www.abcd-study.nl) and the Spanish INfancia y Medio Ambiente (INMA) Project (Guxens et al., 2012) for which we included four INMA sub-cohorts (Valencia, Sabadell, Gipuzkoa, and Menorca). Between 1997 and 2004, depending on the cohort, pregnant women were invited to participate. A total number of 8266 pregnant women for ABCD and 2752 for INMA enrolled and their children have been followed through childhood. RF-EMF exposure and cognitive function were assessed in preadolescents at 9–11 years in ABCD (i.e. Dutch preadolescents) and in the Valencia, Sabadell, and Gipuzkoa sub-cohorts of INMA (i.e. Spanish preadolescents), and in adolescents at 17–18 years in the Menorca sub-cohort of INMA (i.e. Spanish adolescents). We included preadolescents and adolescents with information on RF-EMF exposure and with at least one cognitive test available (n = 1664 (20.1%) Dutch preadolescents, n = 1288 (56.7%) Spanish preadolescents, and n = 261 (54.1%) Spanish adolescents) (Supplementary Figure S1). Informed consent was obtained from all participants as part of the original studies and in accordance with each study's institutional review board.

2.2. Estimated whole-brain RF-EMF dose

We applied an integrative RF-EMF exposure model to estimate whole-brain RF-EMF dose from several RF-EMF exposure sources (Liorni et al., 2020; Luuk van Wel, in press). 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 collected using maternal-reported questionnaires in the Dutch and Spanish preadolescents and self-reported questionnaires in the Spanish adolescents. Duration of i) use of mobile phone for calling, ii) use of DECT phone for calling, iii) mobile phone use for internet browsing, e-mailing, and text messaging (named other mobile phone uses), iv) tablet use while wirelessly connected to internet, and v) laptop use while wirelessly connected to internet was collected in minutes/day.

Information on the proportion of network use for calling, and type of screen activity while other mobile phone uses, laptop use, or tablet use was not collected. 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). During the timeslots where preadolescents and adolescents were using tablet or laptop while wirelessly connected to internet, we assumed that preadolescents and adolescents 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 based on expert opinion.

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 micro-environments where preadolescents and adolescents 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 NISMap was used (Bürgi et al., 2009; Beekhuizen et al., 2013, 2014; Huss et al., 2015). In brief, NISMap computes the field strengths of 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., 2014, 2013; Martens et al., 2015). We assessed the emission of the three mobile phone communication systems in use at the time of the study (GSM900, GSM1800, and UMTS) using a country-wide mobile phone base stations data set from 2015. These systems operated in the following downlink frequency bands: 925–960 MHz, 1805–1880 MHz, and 2110–2170 MHz, respectively. Using the geo-coded address of each participant and the floor level of his/her bedroom at the time of the cognitive function assessment, we computed the RF-EMF exposure from mobile phone base stations at each participant'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 the personal RF-EMF measurements done over up to 72 h by 56 preadolescents from the Dutch cohort and by 191 preadolescents and 53 adolescents from the Spanish cohort (Birks et al., 2018).

2.2.3. *Integrated RF-EMF exposure model*

We applied an integrated RF-EMF exposure model to estimate overall and source-specific whole-brain RF-EMF doses (Liorni et al., 2020; Luuk van Wel, in press). 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 which already takes into account the protection role of the head and individual characteristics (e.g. sex, age, height, weight), known as specific absorption rate (SAR, in Watts (W)/kilogram (kg)), normalized to 1 W output power(Liorni et al., 2020), ii) the output power of each RF-EMF source (in W), and iii) the daily duration of use or exposure to each RF-EMF source (in minutes (min)/day). First, 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 RF-EMF sources) as follows:

$$\text{Specific whole-brain RF-EMF dose}_{source} = \left(\mathbf{SAR}_{source} x\ \mathbf{Output\ power}_{source} x\ \mathbf{Duration}_{source}\right) \qquad \text{Equation 1}$$

Then, overall whole-brain RF-EMF dose was calculated combining the specific RF-EMF doses of all RF-EMF sources:

$$\text{Overall whole-brain RF-EMF dose} = \sum_{source}\left(\mathbf{SAR}_{source} x\ \mathbf{Output\ power}_{source} x\ \mathbf{Duration}_{source}\right) \qquad \text{Equation 2}$$

Moreover, we combined the RF-EMF sources in three groups that lead to different exposure patterns to the brain: i) high RF-EMF doses from peak exposures very close to the head but for short periods of time (i.e. mobile and DECT phone calls, named phone calls), ii) low RF-EMF doses that might mainly represent a variety of social or individual factors related to the use of mobile communication devices (i.e. mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop use while wirelessly connected to the internet, named screen activities), and iii) low RF-EMF doses received continuously throughout the day (i.e. far-field sources such as mobile phone base stations, FM radio and TV broadcast antennas, and WiFi, named far-field).

The output power depends on the characteristics of the network. We assumed that other mobile phone uses, laptop use, and tablet use while wirelessly connected to the internet occur using WiFi at 2.4 GHz and that WiFi data transfer rates were 54 Megabits per second. Moreover, the brain SAR depends on the relative distance to the device. SAR values were estimated in an previous study (Liorni et al., 2020) and we used averaged SAR values from different available positions of use to obtain one SAR value per device and activity that could be inserted in Equation (1) and Equation (2).

2.3. *Cognitive function*

Cognitive function measured as non-verbal intelligence, information processing speed, attentional function, cognitive flexibility, working memory, and semantic fluency were assessed at 9–11 years in the Dutch and Spanish preadolescents or at 17–18 years in the Spanish adolescents using a battery of validated neurocognitive tests (Table 1).

2.3.1. *Non-verbal intelligence*

Non-verbal intelligence describes thinking skills and problem-solving abilities that do not fundamentally require verbal language production and comprehension (Anagnostou et al., 2013). In this study, non-verbal intelligence was assessed using a Raven-like test (Vodegel Matzen et al., 1994) in the Dutch preadolescents and the Raven test (John and Raven, 2003) in the Spanish preadolescents. These tests consist of a matrix of figural patterns in which one pattern is missing. Preadolescents must choose a potential match for the missing pattern from different given options. Over the course of the test, participants were exposed to different matrices, and the task consists on discovering the rules governing the configuration of the patterns and to apply them to select the correct option. The number of correct responses were collected for each cohort, converted into standard deviation units (z-score equals raw score subtracted from mean and divided by the standard deviation) and then standardized to a mean of 100 and a standard deviation of 15 (new score = 100 + 15 x z-score) to homogenize the scores between cohorts. A lower score indicates lower non-verbal intelligence.

2.3.2. *Information processing speed*

Information processing speed is how quick an individual can identify, discriminate, integrate, make decisions, and respond to visual and verbal information (Holdnack et al., 2016). In this study, information processing speed was measured by the coding and the symbol search subtests of the Wechsler Intelligence Scale for Children IV (WISC-IV) in the Spanish preadolescents (Kaufman et al., 2006). In the coding subtest, a clue in which 9 numbers from 1 to 9 are paired with 9 different symbols is given to the preadolescents. Then, preadolescents had to go through a random list of numbers between 1 and 9 and place the corresponding symbol below each number based on the clue given to them at the beginning. They had to do it as fast as possible during a maximum of 120 s. In the symbol search subtest, several rows of 7 symbols, divided in 2 target symbols on the left and 5 other symbols on the right are given to the preadolescents. The preadolescents had to go through each row and identify if one of the 2 target symbols on the left is repeated in the group of 5 symbols on the right as fast as possible during a maximum of 120 s. Scores of the coding and symbol search subsets were summed to form the processing speed index. The processing speed index was converted into standard deviation units (z-score equals raw score subtracted from mean and divided by the standard deviation) and then standardized to a mean of 100 and a standard deviation of 15 (new score = 100 + 15 x z-score). A lower processing speed index indicates lower information processing speed.

2.3.3. *Attentional function*

Attentional function is the capacity to focus on a stimulus over a period of time while ignoring other perceivable information (White et al., 2009). In this study, attentional function was assessed in the Spanish preadolescents and adolescents using the Attention Network Task (Fan et al., 2002). The test consists of responding to whether a central fish placed in the screen is pointing to the left or to the right by

Table 1
Details of cognitive function assessment.

Cognitive ability	Test	Outcome of interest name	Outcome of interest calculation	Interpretation	Cohort and age
Non-verbal intelligence	Raven's Test Raven-like test	Non-verbal intelligence score	Number of correct items	↓n of correct items; lower non-verbal intelligence	Spanish preadolescents Dutch preadolescents
Speed of information processing	Coding and symbol search subtests of the WISC -IV	Processing speed index	Coding subtest score + symbol search subtest score	↓index; lower speed of information processing	Spanish preadolescents
Attentional function	Atentional Network Task	Hit Reaction Time	Mean response time for all correct answer (ms)	↑HRT and ↑omission/commission errors; inattention ↓HRT and ↑omission/commission errors; impulsivity ↑HRT(SE); inattention	
		Hit Reaction Time (Standard Error)	Standard error of the reaction time for responses to all correct answers		
		Omission errors	Number of times the individual did not respond to a stimuli		
		Commission errors	Number of times that the individual respond wrongly		
Visual attention	Trail Making Test-part A	Visual attention score	Time to complete the task (ms)	↑time; lower visual attention	
Cognitive flexibility	Trail Making Test-part B	Task switching score	Time to complete the task (ms)	↑time; lower task switching capacity	
	Trail Making Test-part A and Trail Making Test-part B	Task shifting score	(Time to complete the TMTB (ms) – Time to complete the TMTA (ms))/Time to complete the TMTA (ms))	↑score; lower task shifting capacity	
Semantic Verbal Fluency	Semantic Verbal Fluency Test	Semantic verbal fluency score	Number of words of animals that do not repeat	↓n of words; lower semantic fluency	Spanish preadolescents and adolescents
Working memory	N-back	Hit Reaction Time *d'*	Mean response time for all correct answer (ms) z (hit rate) – z (false alarm rate)	↑HRT and ↓*d'*; lower working memory	

ms, milliseconds; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; WISC-IV, Wechsler Intelligence Scale for Children-IV.

pressing the corresponding button on the mouse while ignoring all the flanking fishes (i.e. the other 4 fish located to the left and right of the central fish), which point in either the same or opposite direction than the central fish. Our primary outcomes of interest were the hit reaction time (HRT, the mean response time in milliseconds (ms) for all correct answer), the standard error of the HRT (HRT(SE), the standard error of the reaction time for responses to all correct answers), the number of omission errors (the number of times the individual did not respond to a stimuli), and the number of commission errors (the number of times that the individual respond incorrectly). Higher omission errors reflect poorer orientation and a slower response. Higher omission errors and/or commission errors together with a fast HRT reflect impulsivity while higher omissions and/or commission errors together with a slow HRT indicate inattention. HRT(SE) is a measure of the consistency of the response time, such that higher values indicate inattention.

2.3.4. *Visual attention*

Visual attention mediates the selection of relevant and the filtering out of irrelevant information from cluttered visual scenes (McMains and Kastner, 2009). Visual attention was assessed in the Spanish preadolescents using the part A of the Trail Making Test (TMTA) (Tombaugh, 2004). Preadolescents were instructed to draw lines connecting 25 consecutive encircled numbers distributed on a computer screen as quickly and accurately as possible. Time to complete the task (in ms) was recorded and higher (i.e. slower) time to complete the task indicates a lower visual attention (Gaudino et al., 1995).

2.3.5. *Cognitive flexibility*

Cognitive flexibility is the ability to switch between thinking about two different concepts, and to think about multiple concepts simultaneously, and can happen unconsciously (task switching) or consciously (task shifting) (Archambeau and Gevers, 2018). Cognitive flexibility was assessed in the Spanish preadolescents using the TMTA (detailed in the previous paragraph) and the part B of the Trail Making Test (TMTB) (Tombaugh, 2004). In the TMTB preadolescents were instructed to draw lines alternating between 13 encircled numbers and 12 letters (from A to L) in an ascending number-letter sequence (1–A–2–B– etc.) distributed on a computer screen as quickly and accurately as possible. Time to complete the task (in ms) was recorded and higher (i.e. slower) time to complete task B indicates a lower task switching capacity. A task shifting score was calculated as follows: ***[TMTB(ms)-TMTA(ms)]/TMTA (ms)]*** (Camelo et al., 2019; Tombaugh, 2004). A higher score indicates a lower task shifting capacity.

2.3.6. *Working memory*

Working memory is the retention of a small amount of information in a readily accessible form (Cowan, 2014). Working memory was assessed in the Spanish preadolescents and adolescents using the N-back test (Pelegrina et al., 2015). Participants were required to respond whenever a stimuli (number) was presented on the screen that matched the one presented 3 trials back. Primary outcomes of interest were HRT (the mean response time in ms for all correct answer), and d prima (d') which allows the distinction of signal and noise taking into account the number of correct rejections, the number of false alarms, the number of hits, and the number of misses (Deserno et al., 2012). d' is indicative of accuracy of the performance of the test and higher HRT and lower d' values indicate lower working memory.

2.3.7. *Semantic verbal fluency*

Semantic verbal fluency involves retrieval of words from conceptual memory (Patterson et al., 2011). Semantic fluency was assessed in the Spanish preadolescents and adolescents using the Semantic Verbal Fluency Test (Sauzéon et al., 2004). Participants had to name in 60 s as many words of animals as they could (Ardila, 2020). The outcome is the number of words that do not repeat. Animals were considered valid if their change of gender or age implied a change of word, or if they referred to fantastic or extinct animals, but animals from the same family scored fewer points. Less number of words indicates a lower semantic fluency.

2.4. Potential confounding variables

The potential confounding variables were a *priori* defined with a Directed Acyclic Graph (DAG) according to the existing literature (Hernan, 2006). Maternal educational level (primary or lower (low), secondary (medium), or university or higher (high)), maternal social class based on the international standard classification of occupations (managers and technicians (high), skilled manual/non-manual (medium), or semi-skilled and unskilled (low)), maternal country of birth (country of the cohort, or others), and maternal smoking during pregnancy (yes or no) were assessed at birth of the child. Maternal anxiety and depressive symptoms were assessed at 5 years of the child using the Depression Anxiety Stress Scale (DASS) (Lovibond and Lovibond, 1995) in the Dutch cohort and the Symptom Checklist-90-Revised (González de Rivera et al., 1989) in the Spanish sub-cohorts of Valencia, Sabadell, and Gipuzkoa. Sex of the child was collected at birth, and age, physical activity, weight, and height were collected or measured at the cognitive function assessment. In the Dutch cohort, physical activity was scored by calculating the Metabolic Equivalent (MET) score for the various reported activities using the compendium of physical activities (Ainsworth et al., 2000) and categorized as low/medium (<percentile 80th) or high (≥percentile 80th). In the Spanish cohort, physical activity was collected in minutes of overall physical activity and categorized as low/medium (≤90 min/day) or high (>90 min/day). Body mass index was calculated as weight/height^2.

2.5. Statistical analysis

After checking that all assumptions of the models were fulfilled, we used a linear mixed-effects model with cohort (i.e. ABCD, INMA-Valencia, INMA-Sabadell, and INMA-Gipuzkoa) as random intercept to assess the association between estimated overall and source-specific whole-brain RF-EMF doses and non-verbal intelligence score. We used linear regression models to assess the association between estimated overall and source-specific whole-brain RF-EMF doses and processing speed index, HRT and HRT (SE) of the Attentional Network Task, visual attention score, task switching score, task shifting score, and HRT and d' of the N-back test, and semantic fluency score. We used negative binomial regression models to assess the association between estimated whole-brain RF-EMF doses and omission errors, and commission errors of the Attentional Network Task. All models were adjusted for potential confounding variables specified in the previous section. Additionally, linear and negative regression models were adjusted for INMA sub-cohort. To assess the influence of the assumptions of the integrated RF-EMF exposure model on our results, we estimated overall whole-brain RF-EMF dose based on two new scenarios slightly modifying our original assumptions and assessed their association with cognitive outcomes in the Dutch and Spanish preadolescents and in the Spanish adolescents. In one scenario (i.e. scenario that lead to a higher RF-EMF exposure), we assumed a proportion of 45% 2G calls, 55% 3G calls, and no hands-free used, and that preadolescents and adolescents were 35% playing video games, 50% streaming video, and 15% browsing the internet or checking social media when using tablet or laptop while wirelessly connected to the internet. In the other scenario (i.e. scenario that lead to a lower RF-EMF exposure), we assumed a proportion of 25% 2G calls, 75% 3G calls, and no hands-free used, and that preadolescents and adolescents were 45% playing video games, 30% streaming video, and 25% browsing the internet or checking social media when using tablet or laptop while wirelessly connected to the internet.

Multiple imputation of missing confounding variables for each cohort/sub-cohort was performed using chained equations where 25 completed datasets were generated and analysed (Nguyen et al., 2017) (Supplementary Table S1). The distributions of the imputed datasets were similar to the non-imputed datasets (data not shown). Of the mother-child pairs recruited initially in the Dutch and Spanish cohorts, Dutch and Spanish preadolescents included in this analysis (n = 1664 and n = 1,288, respectively) were more likely to have had higher weight and gestational age at birth, to have mothers with high level of education and social class at child's birth, and mothers from the country of the cohort, and that had smoked less during pregnancy compared to preadolescents excluded from the Dutch cohort (n = 6227) and from the Spanish cohort (n = 982) (Supplementary Tables S2-S3). Spanish adolescents included in this analysis (n = 261) were more likely to have mothers from high social class and that had smoked less during pregnancy compared to adolescents from the Spanish cohort not included (n = 221) (Supplementary Table S4). Thus, we used inverse probability weighting to correct for loss to follow-up and account for potential selection bias when including only preadolescents or adolescents with available data compared to the full cohort recruited at pregnancy. Variables used to calculate the weights are in Supplementary Table S5.

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

3. Results

3.1. Descriptive analysis

Dutch and Spanish preadolescents of our population had mothers more likely with high level of education, from high social classes, and from the country of the cohort, while Spanish adolescents had mothers more likely with low level of education and from medium social classes (Table 2). Spanish adolescents had a higher estimated overall whole-brain RF-EMF dose (105.4 mJ/kg/day) than the Dutch and Spanish preadolescents (90.1 mJ/kg/day) (Table 3). For Dutch and Spanish preadolescents, and Spanish adolescents, the primary contributor to the

Table 2
Maternal and individual characteristics of the Dutch and Spanish preadolescents, and Spanish adolescents included in our study population.

	Dutch and Spanish preadolescents (n = 2952)	**Spanish adolescents (n = 261)**
Maternal characteristics		
Educational level at child's birth		
High	60.1	16.7
Medium	27.8	31.3
Low	12.1	52.0
Social class based on occupation at child's birth		
High	54.4	20.8
Medium	23.4	65.9
Low	22.2	13.3
Country of birth (country of the cohort vs. others)	88.6	97.7
Anxiety symptoms at 5 years		
(no symptoms vs. at risk or pathological)	47.3	na
Depressive symptomes at 5 years		
(no symptoms vs. at risk or pathological)	37.9	na
Smoking during pregnancy (yes vs. no)	16.3	32.0
Individual characteristics		
Sex (female vs. male)	50.1	52.2
Age at cognitive function assessment, in years	10.0 (1.2)	17.6 (0.2)
Physical activity at cognitive function assessment (low/medium vs. high)	78.9	68.9
BMI at cognitive function assessment, in kg/m2	17.0 (2.5)	22.5 (3.6)

BMI, body mass index; na, data not available. Values are percentages for categorical variables and mean (SD) for continuous variables.

Table 3
Estimated overall whole-brain RF-EMF doses (mJ/kg/day) and contribution of each source-specific dose to the overall whole-brain RF-EMF dose (mean/overall dose, in %) in the Dutch and Spanish preadolescents, and Spanish adolescents.

Whole-brain RF-EMF doses	Dutch and Spanish preadolescents (n = 2952)		Spanish adolescents (n = 261)	
	Median (IQR)		Median (IQR)	
Overall dose	90.1 (42.7; 164.0)		105.4 (51.0; 295.7)	
Source-specific doses		%		%
Phone calls[a]	24.9 (2.1; 80.6)	70.3	83.6 (33.5; 269.8)	96.0
Screen activities[b]	1.4 (0.6; 2.5)	1.3	1.3 (0.1; 2.4)	0.5
Far-field[c]	13.4 (10.1; 32.9)	28.4	11.2 (11.2; 11.2)	3.5

IQR, interquartile range; RF-EMF, Radiofrequency Electromagnetic Fields; mJ, millijoules; kg, kilograms.

[a] Phone calls refer to mobile and DECT phone calls.

[b] Screen activities refer to screen activities with mobile communication devices including mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop while wirelessly connected to the internet.

[c] 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).

overall whole-brain RF-EMF dose was phone calls (70.3% in preadolescents and 96.0% in adolescents), followed by far-field sources (28.4% in preadolescents and 4.7% in adolescents), and screen activities (1.3% in preadolescents and 0.5% in adolescents). Overall whole-brain RF-EMF dose was highly correlated with specific whole-brain RF-EMF dose from phone calls (r = 0.79 in preadolescents and r = 0.88 in adolescents) and specific whole-brain doses had a low correlation between each other (between −0.05 and 0.15 in the Dutch and Spanish preadolescents and between −0.18 and −0.03 in the Spanish adolescents) (Supplementary Table S6). Cognitive outcomes were poorly to moderately correlated with each other in the Dutch and Spanish preadolescents (Supplementary Table S7) and semantic fluency was poorly correlated with working memory in the Spanish adolescents (Supplementary Table S8).

Dutch and Spanish preadolescents having higher overall whole-brain RF-EMF dose, higher dose from phone calls, and higher dose from screen activities were more likely to be older and have mothers from high social class, from foreign countries, and with less anxiety and depressive symptoms (Supplementary Table S9). Dutch and Spanish preadolescents having higher whole-brain RF-EMF dose from far-field sources were more likely to have mothers with a low level of education and from low social class. In the Spanish adolescents, those with higher overall whole-brain RF-EMF dose and higher whole-brain RF-EMF dose from phone calls were more likely to be females and have mothers that smoked during pregnancy (Supplementary Table S10).

3.2. *Estimated whole-brain RF-EMF doses and cognitive function*

In the Dutch and Spanish preadolescents, higher estimated overall whole-brain and specific RF-EMF dose from phone calls were associated with lower non-verbal intelligence score [-0.10 points (95%CI -0.19; −0.02) per 100 mJ/kg/day increase in each exposure] (Table 4). Specific whole-brain RF-EMF doses from screen activities or from far-field sources were not related to non-verbal intelligence score.

Overall and source-specific whole-brain RF-EMF doses were not associated with information processing speed, attentional function, visual attention, and cognitive flexibility in preadolescents, or with working memory and semantic fluency in the Spanish preadolescents and adolescents (Fig. 1, and Supplementary Tables S11-13). Effect estimates showed both positive and negative associations, although they were far from reaching statistical significance.

Table 4
Association between estimated overall and source-specific whole-brain RF-EMF doses and non-verbal intelligence in the Dutch and the Spanish preadolescents (n = 2952).

Whole-brain RF-EMF doses (Δ100 mJ/kg/day)	B (95% CI)
Overall dose	−0.10 (−0.19; −0.02)
Source-specific doses	
Phone calls[a]	−0.10 (−0.19; −0.02)
Screen activities[b]	−18.13 (−37.09; 0.82)
Far-field[c]	0.27 (−0.11; 0.65)

B, Beta Coefficient; CI, confidence interval; kg, kilograms; mJ, millijoules; RF-EMF, Radiofrequency Electromagnetic Fields.
Linear mixed-effects regression models with cohort (ABCD, INMA-Valencia, INMA-Sabadell, INMA-Gipuzkoa) as random intercept adjusted for maternal educational level at child's birth, maternal social class based on occupation at child's birth, maternal country of birth, maternal anxiety and depressive symptoms at 5 years of the child, maternal smoking during pregnancy, and child sex, age, body mass index, and physical activity at cognitive function assessment.

[a] Phone calls refer to mobile and DECT phone calls.

[b] Screen activities refer to screen activities with mobile communication devices includes mobile phone use for internet browsing, e-mailing, and text messaging, tablet use, and laptop while wirelessly connected to the internet.

[c] 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).

3.3. *Sensitivity analysis*

Estimated overall whole-brain RF-EMF dose based on the assumptions of the higher-exposure scenario was 98.8 mJ/kg/day (IQR 50.0; 170.6) in preadolescents and 121.9 mJ/kg/day (IQR 55.0; 362.9) in adolescents and of the lower-exposure scenario was 53.4 mJ/kg/day (IQR 27.2; 118.4) in preadolescents and 78.8 mJ/kg/day (IQR 37.2; 216.1) in adolescents (Supplementary Table S14). All association between the new estimated overall whole-brain RF-EMF doses and cognitive function in the Dutch and Spanish preadolescents and in the Spanish adolescents remained materially unchanged (data not shown).

4. Discussion

Our study investigated the relationship of estimated overall and source-specific whole-brain RF-EMF dose with cognitive function in preadolescents and adolescents. We found that higher overall whole-brain RF-EMF dose and specific whole-brain RF-EMF dose from mobile and DECT phone calls were associated with lower non-verbal intelligence in preadolescents. However, none of the whole-brain RF-EMF doses influenced information processing speed, attentional function, visual attention, and cognitive flexibility in preadolescents. Also working memory and semantic fluency were not affected in both preadolescents and adolescents.

The ability to properly estimate the RF-EMF brain dose from several RF-EMF exposure sources represents an important step forward for the evaluation of the potential effects of RF-EMF exposure in health. Previous studies investigated the relationship of RF-EMF exposure with cognitive function. Nevertheless, most of them did not take into account important factors such as the organ of interest (i.e. the brain), RF-EMF sources other than phone calls (e.g. use of tablets and laptops), position of the RF-EMF source in relation to the body, and personal characteristics (e.g. sex, age, weight, and height). All these factors determine that individuals exposed to same amount of RF-EMF receive different doses to specific organs. The whole-brain RF-EMF dose approach is a recently developed method. Indeed, only one previous cohort study has assessed its association with cognitive function in 12–17 years of age preadolescents and adolescents (Foerster et al., 2018; Roser et al., 2016; Schoeni et al., 2015a). In a longitudinal analysis, the authors found that

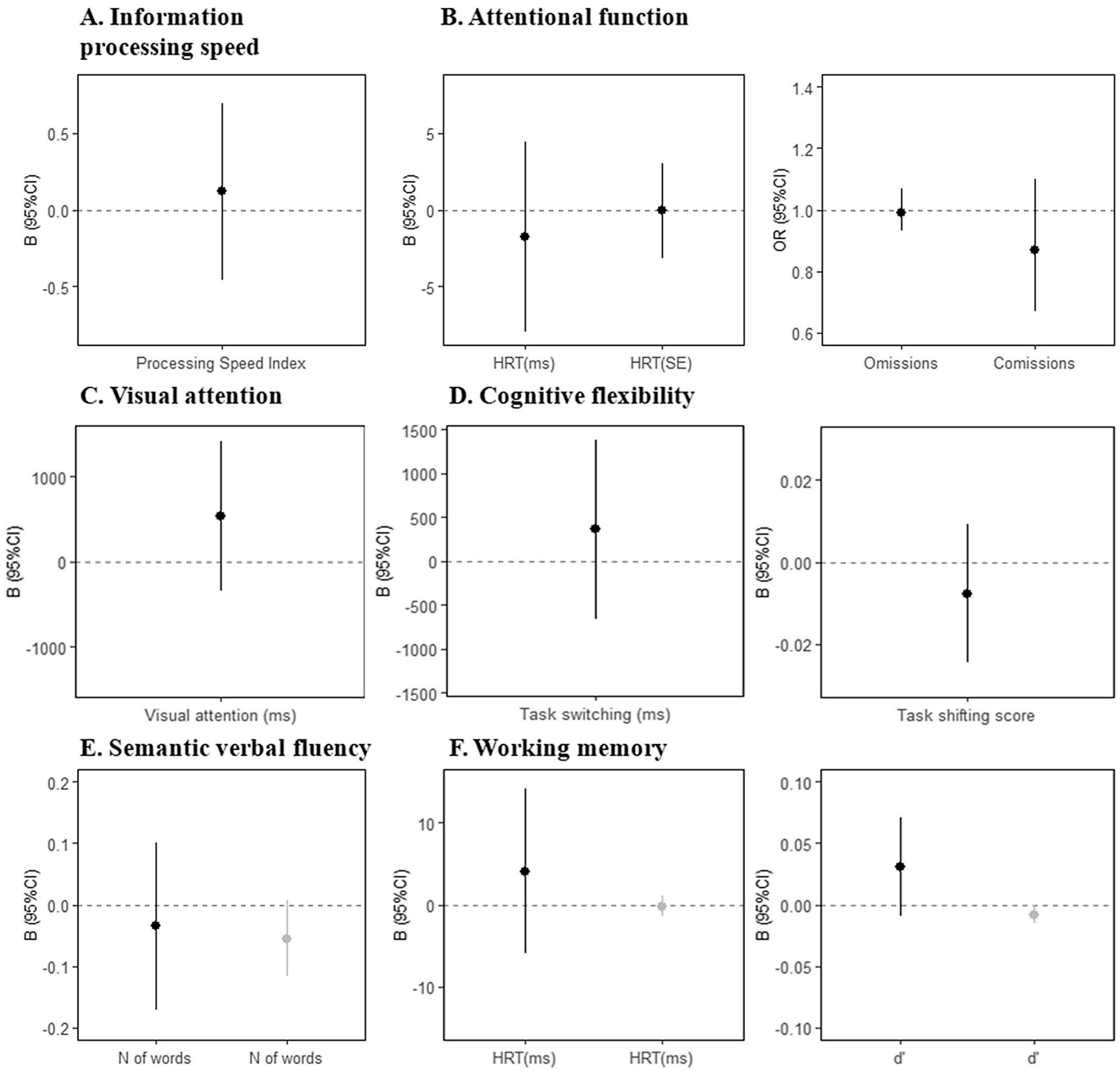

Fig. 1. Association between estimated overall whole-brain RF-EMF dose (per increase of 100 mJ/kg/day) and speed of information processing, attentional function, visual attention, cognitive flexibility, semantic verbal fluency, and working memory in the Spanish preadolescents (black lines, n = 1288) and Spanish adolescents (light grey lines, n = 261).

B, Beta Coefficient; Comissions, commission errors; CI, confidence interval; d', detectability; HRT, Hit Reaction Time (in milliseconds (ms)); HRT (SE), Hit Reaction Time (Standard Error); Omissions, omission errors; OR, odd ratio; TMTA, time to complete part A of the trail making test (in ms); TMTB, time to complete part B of the trail making test (in ms); N of words, number of words. Linear regression models adjusted for maternal educational level, maternal social class based on occupation, maternal country of birth, maternal smoking during pregnancy, child sex, age, body mass index, and physical activity. In preadolescents, linear regression models additionally adjusted for INMA sub-cohort (Valencia, Sabadell, Gipuzkoa) and maternal anxiety and depressive symptoms.

higher whole-brain RF-EMF dose was not associated with concentration capacity (Roser et al., 2016) but was associated with lower figural memory (Foerster et al., 2018; Schoeni et al., 2015a). In a previous study we did not find an association between whole-brain RF-EMF doses and volume alterations in subcortical brain regions involved in memory performance, such as the hippocampus and the amygdala (Cabré-Riera et al., 2020). However, higher RF-EMF exposure induced dendritic remodeling and decrease in viable cells in these subcortical structures in rats (Hussein et al., 2016; Li et al., 2012; Narayanan et al., 2018, 2015, 2010). Although we did not specifically assess figural memory in our study, non-verbal intelligence includes the ability to recognize and remember visual sequences. This ability allows understanding and interpreting the meaning of visual information. Figural memory implies remembering visual information and might be essential to optimally develop non-verbal intelligence, thus we would expect that memory impairments shape deficits in non-verbal intelligence. Also, if there is a true effect of RF-EMF exposure on the brain, as suggested in some experimental studies, cognitive abilities sharing common neural substrates would be similarly affected by RF-EMF exposure. Of note, in our study, we found very small effect estimates in the associations between whole-brain RF-EMF dose and non-verbal intelligence. Therefore, we cannot discard that our results might be due to chance.

No previous studies have assessed the relationship of brain RF-EMF exposure and non-verbal intelligence. Nevertheless, several studies have investigated the association between brain RF-EMF exposure using reported mobile and DECT phone calls, the primary contributors of RF-EMF exposure to the brain (Birks et al., 2018), and other cognitive tasks similar to those included in our study (Abramson et al., 2009; Bhatt et al., 2017; Guxens et al., 2016; Redmayne et al., 2016; Thomas et al., 2010; Zheng et al., 2014). In line with our results, two studies did not show any relationship between number of phone calls and information processing speed (Guxens et al., 2016) or minutes of phone calls with inattention (Zheng et al., 2014) in 5–13 years of age children and preadolescents. However, in contrast to our findings, other studies suggested that higher number of phone calls were related to poorer working memory (Abramson et al., 2009; Thomas et al., 2010), spatial and executive ability (Bhatt et al., 2017), and cognitive flexibility (Guxens et al., 2016) in 5–13 years of age children and preadolescents. Other studies investigated the association between number of phone calls and inhibitory control and visual recognition in 5–13 years of age children and preadolescents, showing mixed results (Abramson et al., 2009; Bhatt et al., 2017; Guxens et al., 2016; Redmayne et al., 2016). The assessment of brain exposure to RF-EMF using reported mobile and DECT phone calls might underestimate the actual brain exposure to RF-EMF since this approach do not take into account other RF-EMF sources that also contribute to the whole-brain RF-EMF dose such as screen activities with mobile communication devices (i.e. mobile phones, tablets, or laptops) wirelessly connected to the internet or far-field sources. This underestimation might be more pronounced in preadolescents than in adolescents since preadolescents make less phone calls but they do more screen activities with mobile communication devices (Birks et al., 2018; Eeftens et al., 2018). The different activity patterns and personal behavior related to the use of mobile communication devices explains dissimilarities in the whole-brain RF-EMF doses from phone calls and screen activities between ages (Eeftens et al., 2018).

The exposure to RF-EMF from far-field sources is mostly explained by distinct characteristics among regions (e.g. deployment of antennas and types of building) (Eeftens et al., 2018). In our study, adolescents were from Menorca, a Spanish Balearic island with lower levels of exposure from far-field sources compared to other regions of Spain (Birks et al., 2018). This fact explains the big differences in the contribution of far-field sources to the overall whole-brain RF-EMF dose between preadolescents and adolescents (28.4% in preadolescents and 4.7% in adolescents). We did not find any relationship between whole-brain RF-EMF dose from far-field sources and cognitive function. On the contrary, one study found that higher residential RF-EMF exposure from mobile phone base stations was associated with improved inhibitory control and cognitive flexibility, and reduced visuomotor coordination in 5-6-year-old children (Guxens et al., 2016).

Nevertheless, all the studies prior to ours did not estimate the RF-EMF dose received by the brain from the different RF-EMF sources. Therefore, it is not possible to assess whether their findings are due to brain exposure to RF-EMF or to social and individual factors related to the use of mobile and DECT phones or to far-field sources. In our study, we could not independently assess whole-brain RF-EMF dose from mobile and DECT phone calls and use of mobile and DECT phones because whole-brain dose from mobile and DECT phone calls and minutes of phone calls were highly correlated ($r > 0.80$). Also, there is growing evidence that mobile communication devices can be beneficial for some cognitive abilities, if prudently used (Wilmer et al., 2017). This beneficial effect could mask potential negative effects of RF-EMF on cognitive function. Consequently, it is key to investigate two main aspects. First, we need to estimate whether the whole-brain RF-EMF dose from phones calls or the use of the phone itself leading to mental arousal, displacement of other activities more beneficial for brain development, or phone dependency among others is behind the observed associations between phone calls and cognitive function (Foerster et al., 2018; Roser et al., 2016; Schoeni et al., 2017, 2015b). Second, we need to assess whether the potential association between phone calls and cognitive function differs between children, preadolescents, and adolescents.

Strengths of this study are the availability of data in almost 3000 preadolescents from two population based birth cohort studies, the assessment of multiple mobile communication devices and cognitive function following similar protocols, and the use of a battery of validated neurocognitive tests. The main limitation of this study is its cross-sectional design. Preadolescents with lower non-verbal intelligence might be more prone to use mobile communication devices, thus, they would be exposed to higher whole-brain RF-EMF dose. To our knowledge, there are no previous studies showing a longitudinal association between lower cognitive function and higher use of mobile communication devices. However, we cannot entirely discard reverse causality. Another limitation might be the fact that in the Dutch cohort we assessed the cognitive function just in terms of non-verbal intelligence and only in preadolescents. Moreover, in the Spanish cohort, we could not evaluate non-verbal intelligence in adolescents. Therefore, we could not investigate whether whole-brain RF-EMF dose was related to non-verbal intelligence in adolescence, age in which brains are more exposed to RF-EMF as adolescents tend to make more phone calls than preadolescents. Furthermore, although we used an innovative and comprehensive tool to estimate whole-brain RF-EMF doses, such method builds on assumptions that could lead to non-differential misclassification of the exposure. This fact could lead to a potential underestimation of the effect. Finally, the use of mobile communication devices was self-reported or reported by the mother. A recent study showed that reported mobile phone use was a valid measure to distinguish between low and high exposed to RF-EMF from mobile phone use (Mireku et al., 2018). Nevertheless, objective measures could be used in new studies to improve accuracy on the measurements of the use of these devices. Such objective measures could be achieved through the use of validated applications installed in participants' mobile communication devices and tracking their actual use.

5. Conclusion

Adolescence is a cognitive demanding stage of life, and one of the most rapid phases of human development. Therefore, it is important to identify factors that could compromise brain development at this stage and permanently impair cognitive abilities. Our results suggest that overall estimated whole-brain RF-EMF dose and specific dose from phone calls were related to lower non-verbal intelligence in preadolescents. However, our findings also indicate that whole-brain RF-EMF doses were not related to information processing speed, attentional function, visual attention, and cognitive flexibility in preadolescents or to working memory and semantic fluency in both preadolescents and adolescents. Given the cross-sectional nature of the study, the small effect sizes, and the unknown biological mechanisms, we cannot discard that our results might be due to chance finding or reverse causality. Our findings open the field to future longitudinal studies to further investigate the association between brain exposure to RF-EMF and cognitive function.

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Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113659.

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