NEW RESEARCH

Exposure to Ambient Temperature and Functional Connectivity of Brain Resting-State Networks in Preadolescents

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Objective: Exposure to extreme temperatures has been linked to acute mental health events in young populations, but the underlying neural mechanisms are not well understood. Resting-state functional magnetic resonance imaging allows for the assessment of connectivity patterns in brain functional networks, which have been associated with mental health disorders. This study investigated the short-term effects of ambient temperature on functional connectivity of brain resting-state networks in preadolescents.

Method: The study was embedded in the Generation R Study, Rotterdam, the Netherlands. Daily mean temperature estimates at the residential addresses of participants were obtained from a high-resolution urban climate model (UrbClim). Resting-state functional connectivity data were assessed with brain magnetic resonance images of 2,229 children ages 9 to 12 years. Distributed lag nonlinear models were fitted to assess the cumulative effects of temperature during the week before the brain scan on within- and between-network connectivity of 15 resting-state networks.

Results: Higher ambient temperature during the week before the imaging assessment was associated with lower functional connectivity within the medial parietal, salience, and hippocampus networks. The effect was highest the day before the brain scan and progressively decayed in the preceding days. Lower temperatures were not related to functional connectivity.

Conclusion: Exposure to high ambient temperatures over a 7-day period was associated with lower within-network connectivity in preadolescents, suggesting impacts of heat on brain function. These findings raise new research questions on whether decreases in functional connectivity within the salience network may partially explain the association between high temperatures and suicide rates previously reported in the literature.

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Climate change is one of the biggest challenges humanity faces. In 2024, the world experienced its warmest year on record, and according to the latest report by the World Meteorological Organization, the global mean temperature is likely to exceed 1.5 °C above preindustrial levels in the next 5 years.[1] In addition, climate change may be contributing to the occurrence of extreme cold events.[2]

Climate change is also a major public health problem. Extreme temperatures can have several harmful effects on human health, including negative impacts on mental health.[3] There is a considerable body of evidence for the short-term impacts of heat on mental health in adults: a recent meta-analysis concluded that increased temperatures may be associated with higher risk of suicide, suicidal behavior, and hospital admissions for mental health disorders.[4] Some studies investigating the short-term effect of temperature on mental health in children observed that higher temperatures were associated with an increase in emergency visits related to acute mental health events,[5-9] specifically due to adjustment disorders in younger children,[5] and anxiety[5,6] and self-inflicted injury/suicide in preadolescents and adolescents.[6] Cold temperatures and unseasonably low temperatures have also been linked to mental health help-seeking behavior in young populations,[5,9] although the literature is not consistent.

The need for research on the mechanisms underlying climate change effects on health, particularly on the brain,[4,10] has been stressed in the literature. Although alterations in brain function have been suggested as potential neural mechanisms linking temperature and mental health, no studies to date have examined the effects of ambient temperatures on brain functional networks. Resting-state functional magnetic resonance imaging (fMRI) is a valuable tool to assess brain function.[11] Resting-state fMRI relies on the blood oxygen level–dependent (BOLD) signal, which measures changes in the relative concentrations of oxyhemoglobin/deoxyhemoglobin. Fluctuations in BOLD signal are linked to neural energy demands and occur even when individuals are not engaged in a particular task, ie, at resting state. Time-series correlation in BOLD signal across different brain regions allows resting-state networks to be defined and functional connectivity (ie, synchronized fluctuations) to be measured within and between these networks.[12] Within- and between-network connectivity values provide complementary information about the segregation and integration of resting-state networks,[13] and differences in within- and between-network connectivity patterns have been observed in a variety of mental health disorders, including anxiety, major depression, and suicide.[14-16] Therefore, we hypothesized that short-term exposure to low and high temperatures may impact resting-state within- and between-network connectivity. We aimed to investigate, for the first time to our knowledge, the effects of short-term ambient temperature on within- and between-network connectivity of resting-state networks in preadolescents.

METHOD

Study Design and Population

This study was embedded in the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands. A total of 9,898 women who gave birth between April 2002 and January 2006 were enrolled in the cohort. Among them, there were 9,607 singleton pregnancies, resulting in 9,503 children born alive (Figure S1, available online). The children and their families were followed from pregnancy onward. All children participating in the cohort at the age of 9 years were invited to undergo a brain MRI assessment between 9 and 12 years. A total of 3,328 children participated in the brain MRI, resulting in 2,515 scans meeting the image quality criteria, which ensured complete brain coverage, minimal motion artifacts, and no major artifacts such as those related to dental retainers. The final study population included 2,229 children who had temperature data for the exposure period of interest. Ethical approval for the study was obtained from the Medical Ethics Committee of the Erasmus Medical Centre in Rotterdam, the Netherlands. Parents completed a written informed consent form to provide consent for themselves and their children.

Temperature Assessment

Temperature estimates were obtained from the urban climate model (UrbClim) developed by the Flemish Institute for Technological Research (VITO).[17] The UrbClim model is composed of a land surface scheme coupled to a three-dimensional atmospheric boundary layer module. It relies on several data sources including land cover, soil sealing, and vegetation maps, and meteorological data from the European Centre for Medium-Range Weather Forecasts Reanalysis v5 (ERA5). The model provides hourly estimates of ambient 2-m temperature at a horizontal resolution of 100 m. Temperature estimates were calculated for the period 2013-2015 in 2 domains of 30 $\times$ 30 km in Rotterdam and surrounding areas. These domains were placed on the location where the maximum number of Generation R participants lived, based on participants' addresses at the time of the imaging assessment. We then assigned daily mean temperature values to each participant based on their residential address starting from the first day up to the seventh day before the MRI assessment, resulting in 7 daily values of temperature per participant. This exposure period was chosen based on previous literature on effects of temperature on acute mental health events.[5,9] Temperature on the day of the MRI assessment was excluded, as more than 50% of MRI scans were conducted before noon. Therefore, the daily mean temperature for that day would mostly reflect exposure occurring after the outcome assessment.

Even though the UrbClim model has been validated in different locations, we conducted a validation against observed data for our specific location and period of interest. We used temperature station data from the European daily gridded land-only observational dataset (E-OBS),[18] collected in 4 local monitoring stations within the 2 domains of interest (Voorschoten, Valkenburg, Rotterdam, and Rotterdam-Geulhaven). The R^2 of the model was 0.971, and the root mean square error was 1.02 °C (Figure S2, available online).

Resting-State MRI Assessment

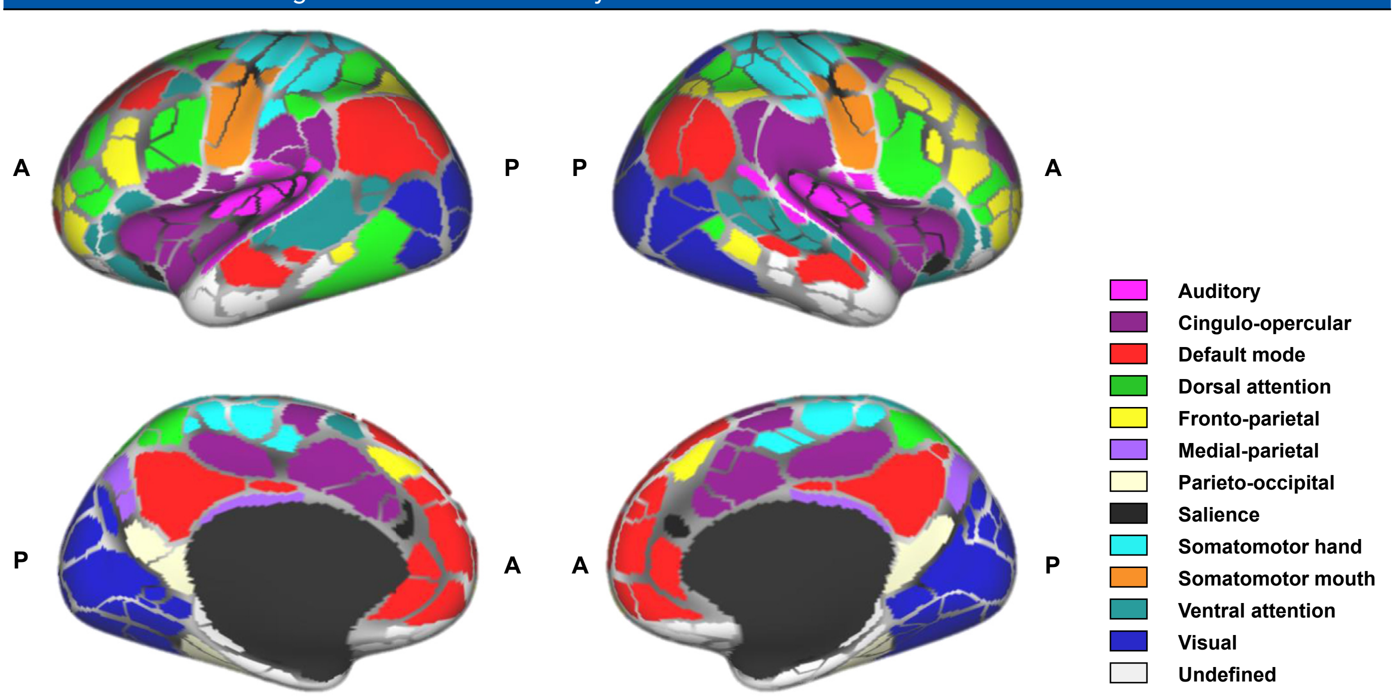
All scans were conducted at the Erasmus University Medical Centre in Rotterdam using a 3.0T Discovery MR750W scanner (GE HealthCare, Milwaukee, Wisconsin) with an 8-channel receive-only head coil. Before the actual MRI session, all children underwent a mock scanner session to familiarize them with the procedure. The actual MRI session included a brain resting-state fMRI scan, during which participants were instructed to stay awake with their eyes closed. The resting-state fMRI data were preprocessed using the standardized fMRIPrep (singularity image, version 20.2.7) software.[19] Information on sequence parameters, preprocessing, and quality control process is provided in Methods S1 (available online) and have been published elsewhere.[20] Functional connectivity values were calculated based on Gordon's parcellation,[21] which defines 333 cortical regions grouped into 13 resting-state networks: auditory, cingulo-opercular, default mode network, dorsal attention, frontoparietal, medial parietal, parieto-occipital, salience, somatomotor hand, somatomotor mouth, ventral attention, visual, and an undefined network (Figure 1). This last network reflects connectivity in areas located in none of the other networks. As the amygdala and hippocampus seem to be particularly susceptible to environmental stressors,[22] we also included these 2 subcortical regions in the analysis, which were defined based on FreeSurfer subcortical segmentation.[23].

Cerebrospinal fluid and white matter signals as well as motion parameters (and their quadratic terms and temporal derivatives) were regressed out from the data. For each participant, time-series correlation in BOLD signal was estimated pairwise for the 333 cortical and 2 subcortical regions, and the Pearson correlation values were Fisher z-transformed to normalize the data. Within-network connectivity was defined as the average correlation among all regions within each network. For example, if regions 1 to 3 belong to the same network, we calculated the average of the correlations between region 1 and region 2, region 1 and region 3, and region 2 and region 3 to determine the within-network connectivity for that network. Similarly, between-network connectivity was defined as the average correlation between regions belonging to a first network and regions belonging to a second network (eg, if regions 1-3 comprise network A and regions 4-6 comprise network B, we averaged the correlations between regions 1 and 4, 1 and 5, 1 and 6, 2 and 4, 2 and 5, 2 and 6, and so on, to calculate connectivity between networks A and B).

Confounding Variables

Selection of confounding variables was based on previous research,[24–26] data availability, and a directed acyclic graph (Figure S3, available online). Questionnaires were used to collect socioeconomic characteristics of the families at 3 time points: pregnancy visit (enrollment), follow-up visit when children were around 5 years old (visit age 5), and follow-up visit when children were around 9 years old (visit age 9). Information collected at enrollment included parental age, parental national origin (Morocco, other countries from the Global North, other countries from the Global South, Suriname/Dutch Antilles, the Netherlands, and Turkey) and maternal marital status (partner vs single). At visit age 5, information on parental educational level (high, medium, low), number of children living in the house (1 child, 2 children, 3 children or more), and maternal employment status (employed, self-employed, and unemployed) was collected. Questionnaires at visit age 9 asked about monthly household income (less than €2,000, €2,000-€3,200, €3,200-€4,400, greater than €4,400), type of housing tenure (owned vs rented), and financial difficulties (difficulties paying the bills no vs yes). In

FIGURE 1 Cortical Resting-State Networks defined by Gordon's Parcellation



Note: *A = anterior; P = posterior. Adapted from Gordon et al., 2016.[21] Please note color figures are available online.*

addition, we used a neighborhood socioeconomic status (SES) indicator, based on the average educational level, income, and labor market position of the population in the same postal code area during the year 2014, provided by Statistics Netherlands. To account for the potential influence of greenness exposure, we included the normalized difference vegetation index within a radius of 300 m from the residential address for the year before the outcome assessment. The higher the values of normalized difference vegetation index, the denser the vegetation in the residential surroundings. To account for seasonal patterns, we included the month of the MRI assessment. Finally, we also included 2 important determinants of the outcome: child sex, obtained from the medical records, and child age at the MRI assessment. We did not adjust for air pollution because we considered it a possible mediator in the association of interest.[27]

Statistical Analysis

The final study population consisted of 2,229 children with information on the exposure and outcome. The percentage of missing values was less than 21% for all confounding variables (Table S1, available online). We used the expectation-maximization algorithm to impute missing values in these confounding variables, obtaining 1 imputed dataset with covariate distributions similar to the observed distributions. However, the study population and the participants not included (7,378 participants) differed in some characteristics (Table S2, available online). To mitigate potential selection bias, we performed an inverse probability weighting using the covariate balancing propensity score technique. In brief, we calculated the probability of being included in our study given a set of covariates, and we used the inverse of this probability as weights in the analysis, assigning a greater weight to children with characteristics that were underrepresented in the study population (Methods S2, available online).

We applied distributed lag nonlinear models (DLNMs)[28] to estimate the cumulative effect of temperature over 7 days on within- and between-network connectivity of the 13 cortical networks and 2 subcortical regions. The model included temperature exposure from lag-1 to lag-7, with lag-1 as the day before the MRI assessment. DLNMs were fitted through generalized linear models. We compared different DLNM parametrizations for the exposure-response relation and lag-response relation, based on the Akaike information criterion. For the exposure-response relation, we compared 3 parametrizations: 2 knots at 25th and 75th percentiles; 2 knots at 10th and 90th percentiles; and 3 knots at 10th, 50th, and 90th percentiles. In the lag-response relation, we considered a linear fit, 1 knot at the middle lag (lag-4) and 1 knot in the middle lag on the logarithmic scale (lag-2.5). Given that we had 120 outcomes, the best model was not the same for all the outcomes, but the differences in the Akaike information criterion were minimal. Thus, we made parsimonious decisions a priori and explored alternative parametrization as sensitivity analyses. In the main analysis, we used natural splines and placed 2 knots at 25th and 75th percentiles in the exposure-response relation. The lag-response relation was modeled as linear. We added an intercept in the lag-response as we did not expect a null effect at the beginning of the lag-period. The reference temperature was the median value of temperature distribution over the 7-day period for all participants (13.7 °C). As we had multiple outcomes for both within- and between-network connectivity, we applied multiple testing correction following Galwey's methodology. For the 15 within-network connectivity outcomes, the obtained effective number of tests was 12, which resulted in a p value of .00417 (.05/12). For the 105 between-network connectivity outcomes, the effective number of tests was 49, which resulted in a p value of .00102 (.05/49). The lag-response curves were plotted only when cumulative effects remained significant after multiple testing correction. All models were adjusted for the above-mentioned confounders.

In addition, we performed several follow-up and sensitivity analyses of the associations identified in the main analysis. First, we repeated the analysis using daily minimum and maximum temperatures as exposures to determine whether one of them was primarily driving the results. Second, to assess the effects of unseasonably high and low temperatures, we performed a sensitivity analysis stratifying by season, following the approach of Sugg *et al.*[9] Seasons were defined according to the meteorological calendar: the cold season included data from September to February, and the warm season included data from March to August, based on the month of the MRI assessment. Third, we explored the role of some covariates as effect modifiers in the association, stratifying the analysis for neighborhood SES, residential surrounding greenness, and child sex. Fourth, we fitted DLNMs with alternative model parametrizations to test the robustness of our findings, as explained above. Fifth, we performed a sensitivity analysis using a more stringent multiple testing correction, based on the effective number of tests considering all the within- and between-network connectivity outcomes, ie, 120 outcomes, corresponding to 57 effective number of tests and a p value of .00088 (.05/57). Finally, we conducted a sensitivity analysis using resting-state fMRI connectivity data with the global signal regressed out. Global signal refers to an overall signal intensity captured across the whole brain as a consequence of both neural fluctuations and non-neural fluctuations, such as changes in blood flow, arterial CO_2, or respiratory activity. Global signal regression removes the non-neural sources of noise, while also removing neural fluctuations that may be part of functional connectivity of the resting-state networks, which makes this approach controversial.[29] However, there is no clear consensus in the fMRI field on the preferred methodology. For that reason, we tested the robustness of our findings using this alternative approach.

Statistical analyses were performed in R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). We used the amelia package for expectation-maximization imputation, the CBPS package for the covariate balancing propensity score procedure, the dlnm package for the DLNM analysis, and the poolr package for the calculation of the effective number of tests.

RESULTS

Study Population

The mean (SD) age of children at the MRI assessment was 10.1 (0.6) years old (Table 1). Most families were composed of 2 adults and 2 or more children, and most parents were born in the Netherlands and had a high level of education. Mean daily temperatures over the 7-day period at the places of residence of participants ranged from −2.1 °C to 29.7 °C, with the distribution by season and year shown in Figure 2. Descriptive plots of the within- and between-network connectivity values are provided in the supplement (Figures S4 and S5, available online).

Main Analysis

Compared with the reference temperature (13.7 °C), higher daily mean temperatures were associated with lower within-network connectivity in the cingulo-opercular, medial parietal, salience, and undefined networks, and in the hippocampus (Figure 3). Compared with the reference temperature, lower temperatures were associated with lower within-network connectivity in the parieto-occipital and somatomotor mouth networks.

After multiple testing correction, only the associations between high temperature and within-network connectivity in the medial parietal network, salience network, and hippocampus remained statistically significant. Specifically, daily mean temperatures between 17.7 °C and 23.8 °C over a 7-day period were associated with lower functional connectivity within the medial parietal network (eg, $\beta = -.05$ [95% CI −0.08 to −0.02] at 21.8 °C, ie, at the 95th percentile of temperature distribution). Daily mean temperatures between 18.4 °C and 25.5 °C over a 7-day period were associated with lower functional connectivity within the salience network (eg, $\beta = -.05$ [95% CI −0.07 to −0.02] at 21.8 °C). Lastly, daily mean temperatures between 20.4 °C and 23.0 °C over a 7-day period were associated with lower functional connectivity within the hippocampus (eg, $\beta = -.05$ [95% CI −0.09 to −0.02] at 21.8 °C). The effect was highest the day before the MRI scan and progressively decayed in the days before (Figure 4). Regarding the effects on between-network connectivity (Figure S6, available online), no association survived any multiple testing correction threshold.

Follow-Up and Sensitivity Analysis

Both higher daily minimum and maximum temperatures were associated with lower within-network connectivity in the medial parietal network, salience network, and hippocampus, with effect estimates being slightly higher for daily maximum temperatures (Figure S7, available online). The stratified analysis by season showed lower within-network connectivity values associated with higher daily temperatures in both cold and warm seasons, especially for the salience network, where confidence intervals did not include the null in either season (Figure S8, available online). We did not observe a clear modification of the effect by neighborhood SES, residential surrounding greenness level, or child sex. Although some CIs were wider, the pattern of lower within-network connectivity at higher temperatures remained consistent across all groups for the 3 networks identified in the main analysis (Figures S9-S11, available online). We observed very similar cumulative effects of high temperatures on the medial parietal network, salience network, and hippocampus within-network connectivity using the alternative DLNM parametrizations (Figures S12-S14, available online). Using a more stringent multiple testing correction ($p = .00088$), hotter temperatures were associated with lower functional connectivity within the medial parietal and salience networks, but the association disappeared for the hippocampus (Figure S15, available online). Finally, in the sensitivity analysis regressing out the global signal, we identified similar associations between high temperatures and within-network connectivity values of the medial parietal and salience networks, although the estimated effects were attenuated (Figure S16, available online).

DISCUSSION

Exposure to high daily mean temperatures the week before the MRI assessment was associated with lower within-network connectivity in the medial parietal network, the salience network, and the hippocampus. In the lag-response association, the greatest effect was observed the day before

TABLE 1 Characteristics of Study Population (N = 2,229)

	Values	
	%	
Child characteristics	Mean	(SD)
Sex, female vs male	51.5	
Age at MRI, y	10.1	(0.6)
Child Behavior Checklist for Ages 6-18 at visit age 9		
Internalizing problems score[a]	5.1	(4.9)
Externalizing problems score[b]	3.9	(4.4)
Attention problems score[c]	3.1	(2.9)
Maternal characteristics	Mean	(SD)
Age at enrollment, y	31.1	(4.9)
	%	
National origin		
Morocco	5.7	
Other countries from the Global North	8.6	
Other countries from the Global South	13.9	
Suriname/Dutch Antilles	9.4	
The Netherlands	55.7	
Turkey	6.7	
Marital status at enrollment partner vs single	88.4	
Educational level at visit age 5		
High	57.6	
Medium	30.0	
Low	12.4	
Employment status at visit age 5		
Employed	64.2	
Self-employed	12.3	
Unemployed	23.4	
Partner characteristics	Mean	(SD)
Age at enrollment, y	33.7	(5.8)
	%	
National origin		
Morocco	6.2	
Other countries from the Global North	6.3	
Other countries from the Global South	13.4	
Suriname/Dutch Antilles	10.0	
The Netherlands	57.2	
Turkey	6.9	
Educational level at visit age 5		
High	53.4	
Medium	29.7	
Low	16.9	
Household characteristics at visit age 9		
Number of children living in the house		
1 child	18.4	
2 children	53.7	
≥3 children	27.9	
Monthly household income, €		
>4,400	27.9	
3,200-4,400	26.8	
2,000-3,200	22.3	
<2,000	23.0	
Housing tenure, owned vs rented	76.4	
Financial difficulties, no vs yes	79.9	
	Mean	(SD)
Neighborhood SES[d]	−0.1	(0.2)
Residential surrounding greenness level[e]	0.4	(0.1)

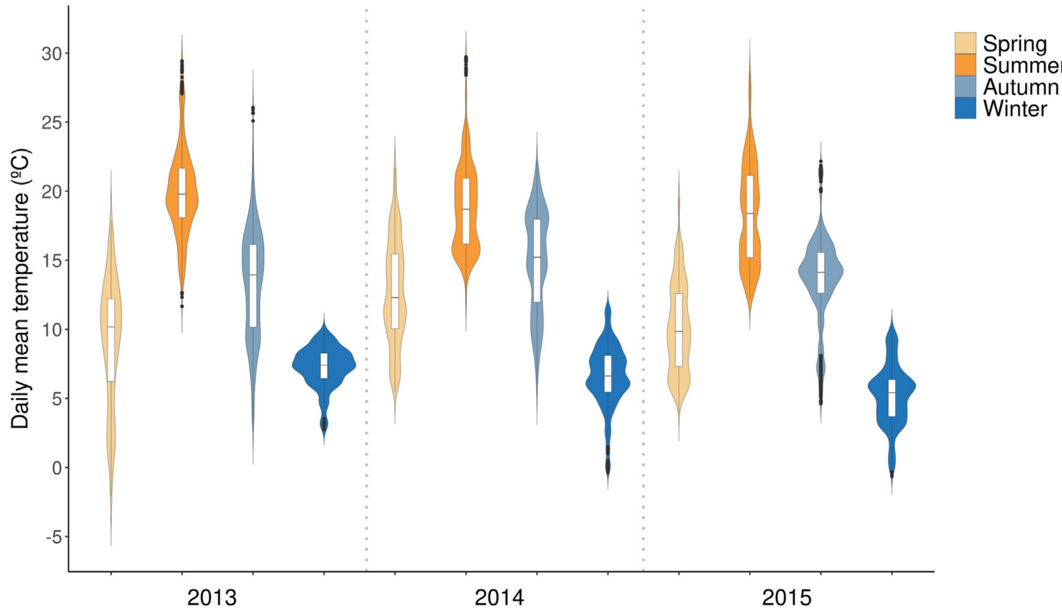
Note: MRI = magnetic resonance imaging; SES = socioeconomic status.
[a]*Ranging from 0 to 37.*
[b]*Ranging from 0 to 38.*
[c]*Ranging from 0 to 18.*
[d]*Ranging from −0.4 to 0.3.*
[e]*Ranging from 0.1 to 0.7.*

the scan, diminishing progressively in the days before. Low daily mean temperatures were not related to functional connectivity.

No studies have yet investigated the effects of ambient temperatures on functional connectivity of brain networks, although a few have explored the effects of simulated hyperthermia on some resting-state functional networks. Sun *et al.*[30] compared resting-state functional connectivity of 36 participants exposed to 25 °C for an hour with the same participants exposed to 50 °C. They identified decreases in the functional connectivity within the posterior cingulate and precuneus networks when the participants were exposed to hyperthermia.[30] Although the authors of this study considered these regions part of the default mode network, our definition of medial parietal network includes part of these anatomical regions.[21] In another study, similar hyperthermia conditions decreased within-network connectivity in the anterior nodes of the default mode network, such as the medial prefrontal and anterior cingulate cortices.[31] Comparing our results with these previous studies is challenging, as 1 hour at hyperthermia in experimental conditions is a very extreme and short exposure compared with 7 days daily mean ambient temperatures, and their effects may be very different.

Our findings indicate that short-term exposure to high ambient temperatures is associated with diminished connectivity within the medial parietal network. Anatomically, this network corresponds to the posterior-medial portion of the parietal lobe, which integrates diverse information sources to represent the body and peripersonal space, enhancing self-referential processes.[32] This region is

FIGURE 2 Temperature Distribution Over the 7-Day Period at the Participants' Places of Residence by Season and Year

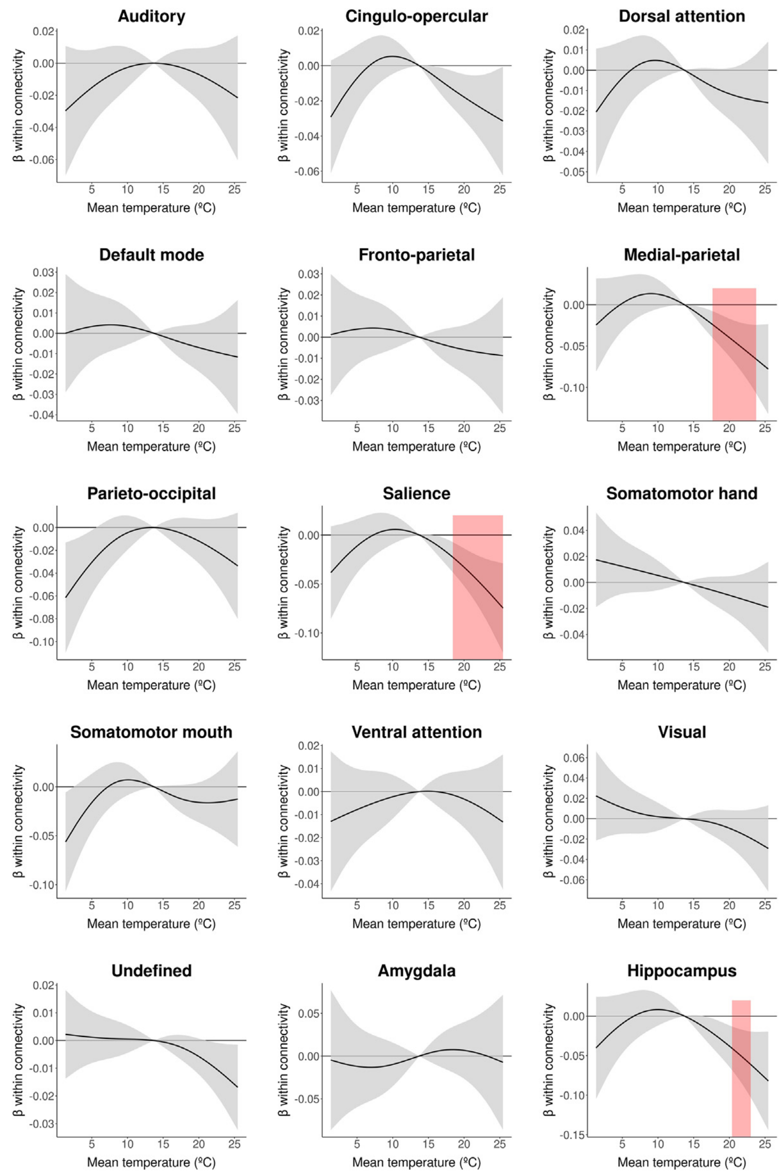


Note: *Boxplots within the violin plots show the median and interquartile range. Upper and lower boundaries of the violin plots represent the maximum and minimum values, respectively. Width of the violin plots represents the density of observations at that temperature value. Based on the month of the magnetic resonance imaging scan and following the meteorological calendar, spring includes March to May, summer includes June to August, autumn includes September to November, and winter includes December to February. Please note color figures are available online.*

essential for advanced visuospatial and semantic representations of the body and self as well as for the experience of body ownership and autobiographical memory.[33] Furthermore, the medial parietal cortex is crucial in extending self-perception to include perspective taking and consideration of others,[34] and it plays a role in cognitive functions such as theory of mind.[32]

Short-term exposure to high ambient temperatures was also associated with lower functional connectivity within the salience network in early adolescence. The salience network is responsible for detecting and responding to internal and external stimuli important for addressing homeostatic imbalances. It assigns emotional values to these stimuli and plays a role in regulating emotions across various situations.[35] Meta-analytical data identified within-network hypoconnectivity in the salience network in a variety of psychiatric disorders, including attention-deficit/hyperactivity disorder, anxiety, bipolar disorder, and major depressive disorder.[14] Additionally, based on data from 63 studies, Zhang *et al.*[36] identified the salience network as 1 of the 3 networks altered in individuals with suicidal behavior. In adolescents, resting-state fMRI studies have also highlighted the role of the salience network in suicide. For instance, lower coherence within the salience network—defined as the strength of within-network connectivity—has been associated with greater severity of suicidal ideation among adolescents with major depressive disorder[37] and with reporting suicide ideation and self-injury behaviors in depressed adolescents compared with depressed adolescents without these behaviors and healthy control participants.[38] In addition, a longitudinal study found that decreases in suicidal ideation corresponded to increases in the coherence within the salience network.[39] Short-term high ambient temperatures have consistently been associated with suicide risk in different locations around the world,[40] but the underlying mechanisms are not clear. Interestingly, the stratified analysis by season showed an association between higher temperatures and lower connectivity within the salience network in both the cold and the warm seasons. This suggests that not only absolute high temperatures negatively affect the salience network, but also unseasonably high temperatures, similarly to what has previously been identified for suicide and other acute mental health events.[4] Considering the role of the salience network in suicidal ideation, our findings give rise to a new hypothesis: functional connectivity decreases within the salience network may partially explain the association between high temperature and suicide rates reported in the literature. As we explored the short-term effects of temperature, we do not propose that temperature effects on the salience network directly induce suicidal behaviors. However, we hypothesize that high temperatures might trigger suicide attempts in

FIGURE 3 Cumulative Associations Between Temperature Exposure Over a 7-Day Period and Within-Network Connectivity in 13 Resting-State Networks and 2 Subcortical Regions

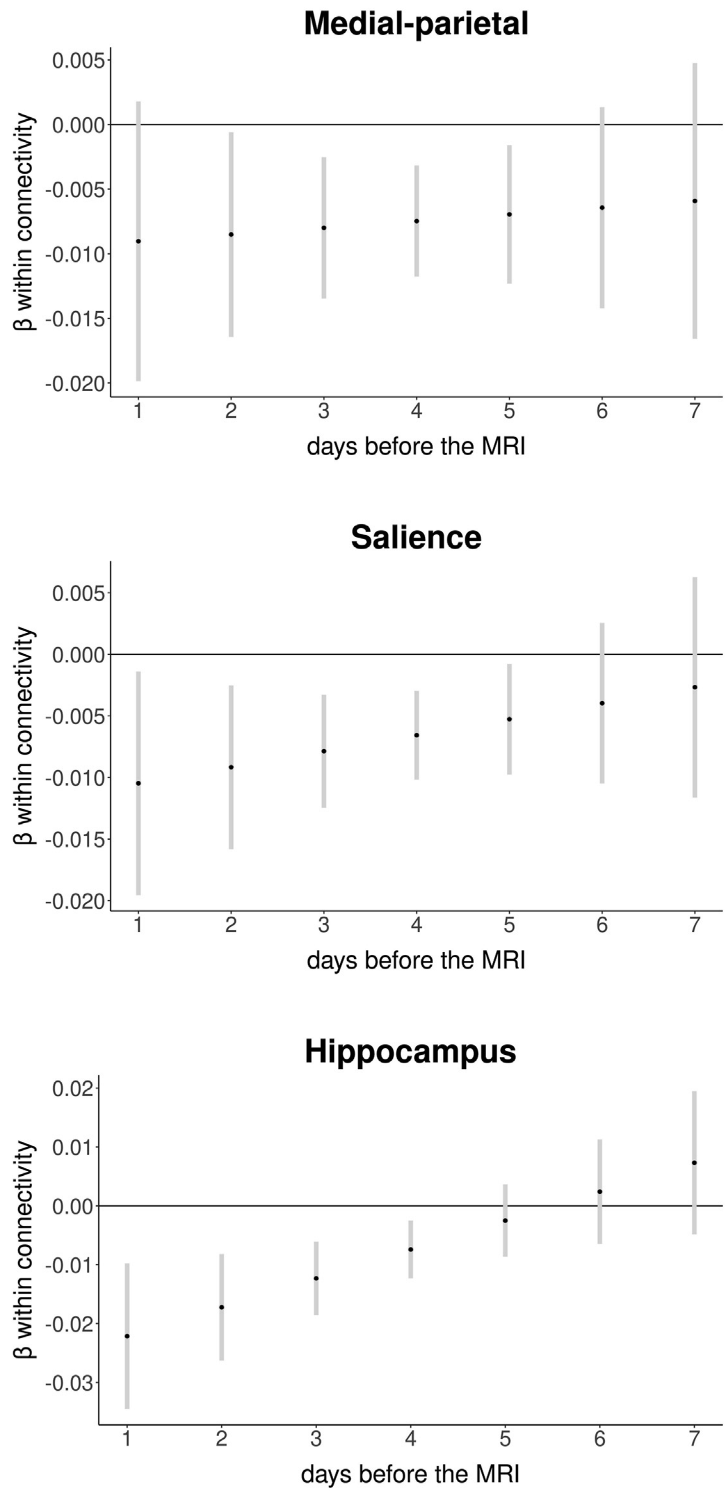


Note: *Cumulative associations (black line) and 95CIs (gray area) were obtained from distributed lag nonlinear models. Temperature ranges for which associations survived multiple testing correction are highlighted in red (*$p \leq .00417$*). Models were adjusted for child's sex and age at magnetic resonance imaging assessment; maternal age, educational level, national origin, marital status, and employment status; paternal age, national origin, and educational level; household income, number of children living in the house, housing tenure, and financial difficulties; and neighborhood socioeconomic status, residential surrounding greenness level, and month of magnetic resonance imaging assessment. Please note color figures are available online.*

individuals with preexisting mental health disorders by impacting this network.

Short-term exposure to high ambient temperature was associated with lower connectivity within the hippocampus. The role of the hippocampus in learning and memory is well established.[41] At the same time, the hippocampus is part of the limbic system, which provides psychological and behavioral responses to environmental stressors, and it contributes to the regulation of the hypothalamic-pituitary-adrenal axis.[42] Due to its role in stress response, the hippocampus learning and memory functions are susceptible to disruption by external stressors.[43] In animal models, short-term exposure to hyperthymic conditions was shown to negatively impact the hippocampus, increasing oxidative stress markers, inducing neuronal loss and apoptosis, and leading to memory impairments in mice.[44,45] In humans,

FIGURE 4 Association Between the 95th Percentile of Temperature Distribution and Within-Network Connectivity in the Medial Parietal Network, Salience Network, and Hippocampus for the 7 Days Before Magnetic Resonance Imaging (MRI) Assessment



Note: Lag-response associations (dots) and 95% CIs (vertical lines) were obtained from distributed lag nonlinear models. Models were adjusted for child's sex and age at MRI assessment; maternal age, educational level, national origin, marital status, and employment status; paternal age, national origin, and educational level; household income, number of children living in the house, housing tenure and financial difficulties; and neighborhood socioeconomic status, residential surrounding greenness level, and month of MRI assessment.

memory could be also affected by heat exposure, as short-term exposure to high ambient temperatures has been associated with worse cognitive performance, including impairments in working memory tasks.[46] However, these results should be taken with caution as the observed association between high temperatures and functional connectivity in the hippocampus disappeared in the sensitivity analysis using a more stringent multiple testing correction.

One possible mechanism explaining our findings is dehydration, as children are particularly susceptible to fluid loss when exposed to heat,[47] and this can affect the functional connectivity of brain networks in adolescents.[48] In addition, the results were driven not only by high maximum but also by high minimum daily temperatures, ie, high nighttime temperatures, suggesting that sleep deprivation may be a potential mechanism in the association. In a recent systematic review, it was concluded that high temperatures tend to be linked to lower sleep quality in adults,[49] an effect that has also been observed in preadolescents.[50] Concurrently, Ben Simon *et al.*[51] found that sleep deprivation in young participants led to reductions in modularity in the salience network, which result from a decrease in the number of connections within the salience module and an increase in connections between the salience network and other modules.

We examined the role of neighborhood SES, residential greenness level, and sex as potential effect modifiers in the association between temperature and brain functional connectivity, as these covariates have previously been identified as modifiers in the association between heat and mental health disorders.[52,53] However, in our study, we did not observe a consistent pattern of effect modification by these factors. From a public health perspective, it is crucial to further investigate the role of social determinants of health in this association. Future research should consider collecting data on household insulation quality, access to cooling resources, energy affordability, and green space use to better identify children most vulnerable to the effects of high temperatures.

The strengths of this study include the large sample size and data collection on several socioeconomic characteristics, which allowed us to control for confounding variables in the analysis. Regarding the exposure assessment, we used physically consistent temperature data at a very high spatial and temporal resolution, successfully validated against observed data. For the outcome assessment, we addressed the lack of consensus on the global signal regression in resting-state fMRI studies through a sensitivity analysis. Finally, the statistical approach, ie, DLNMs, allowed us to assess the nonlinear and delayed effects of temperature exposure.

Some limitations of the study warrant discussion. First, our exposure assessment included only temperature estimates at the residential level, as we did not have temperature data at schools. Future studies investigating temperature effects on school-age populations should consider temperature at schools, especially studies aiming to develop prevention strategies and public health policies. Although the absence of indoor temperature data is a limitation, considering the Dutch context where the availability of heating is much higher than that of air conditioning,[54] we believe this limitation may have underestimated the effects of cold exposure, whereas it has less impact on estimations of heat effects. Second, we lacked information to confirm that children were at their residential address during the 7 days preceding the MRI assessment, which could lead to misclassification of the exposure. Regarding outcome assessment, the lack of established normal and abnormal thresholds for within- and between-network connectivity values complicates their clinical interpretation. Additionally, there are some limitations associated with using Gordon's parcellation as an atlas for defining brain functional networks. This parcellation scheme differs from others used in the literature; therefore, a fair comparison of our findings with those from studies using other methods is not entirely guaranteed. Moreover, similar to other schemes, Gordon *et al.*[21] defined resting-state networks in adults, meaning this parcellation may not align perfectly with the brain of a child. Regarding the statistical analysis, DLNMs might be sensitive to different parametrizations, although the sensitivity analysis showed consistent results. Finally, although we used inverse probability of participation weighting to mitigate selection bias, some important variables such as parental health literacy level were not accounted for. Additionally, although we adjusted all models for several confounders, the variables used as proxies for SES might have been insufficient, and residual confounding cannot be ruled out.

In conclusion, exposure to high daily ambient temperatures over a 7-day period was associated with lower within-network connectivity in the medial parietal network, the salience network, and the hippocampus, suggesting an impact of short-term heat exposure on brain function in preadolescents. Considering the role of the salience network in suicide, these findings raise new research questions on whether decreases in functional connectivity within the salience network may partially explain the association between high temperatures and suicide rates previously reported in the literature. Low daily temperatures over a 7-day period were not related to the functional connectivity of brain networks in our study. In the ongoing climate change emergency, public health policies aimed at protecting children and adolescents from high temperatures may contribute to reducing their potential impacts on brain function. Future research should explore the mediator role of functional connectivity of brain networks in the association between short-term heat exposure and acute mental health events to better understand the neurological basis of negative impacts of temperature on mental health.

CRediT authorship contribution statement

Laura Granés: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Michelle S.W. Kusters:** Writing – review & editing, Visualization, Validation, Methodology. **Joan Ballester:** Writing – review & editing, Methodology. **Esmée Essers:** Writing – review & editing, Methodology. **Sami Petricola:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Mónica López-Vicente:** Writing – review & editing, Data curation, Methodology. **Carmen Iñiguez:** Writing – review & editing, Methodology. **Henning Tiemeier:** Writing – review & editing, Methodology, Funding acquisition, Investigation, Resources. **Ryan L. Muetzel:** Writing – review & editing, Resources, Methodology, Funding acquisition, Data curation, Investigation. **Carles Soriano-Mas:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization, Writing – original draft. **Mònica Guxens:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

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The research was performed with permission from the Generation R Management Team.

Consent has been provided for descriptions of specific patient information.

The authors have reported the use of ChatGPT to correct English grammar.

Data Sharing: The datasets generated and analyzed during the current study are not publicly available due to legal and ethical regulations, but may be made available upon request to the Director of the Generation R Study, Vincent Jaddoe (secretariaat.genr@erasmusmc.nl), in accordance with the local, national, and European Union regulations.

The code to reproduce the analysis is available at the open repository dataverse of the Consorci de Serveis Universitaris de Catalunya (CSUC), under https://doi.org/10.34810/data1845

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