

## RESEARCH ARTICLE

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# Lifestyle risks associated with brain functional connectivity and structure

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## Abstract

Some lifestyle factors are related to health and brain function and structure, but the brain systems involved are incompletely understood. A general linear model was used to test the associations of the combined and separate lifestyle risk measures of alcohol use, smoking, diet, amounts of physical activity, leisure activity, and mobile phone use, with brain functional connectivity with the high resolution Human Connectome Project (HCP) atlas in 19,415 participants aged 45–78 from the UK Biobank, with replication with HCP data. Higher combined lifestyle risk scores were associated with lower functional connectivity across the whole brain, but especially of three brain systems. Low physical, and leisure and social, activity were associated with low connectivities of the somatosensory/motor cortical regions and of hippocampal memory-related regions. Low mobile phone use, perhaps indicative of poor social communication channels, was associated with low functional connectivity of brain regions in and related to the superior temporal sulcus that are involved in social behavior and face processing. Smoking was associated with lower functional connectivity of especially frontal regions involved in attention. Lower cortical thickness in some of these regions, and also lower subcortical volume of the hippocampus, amygdala, and globus pallidus, were also associated with the sum of the poor lifestyle scores. This very large scale analysis emphasizes how the lifestyle of humans relates to their brain structure and function, and provides a foundation for understanding the causalities that relate to the differences found here in the brains of different individuals.

## KEYWORDS

brain structure and functional connectivity, diet, drinking, hippocampus, lifestyle, orbitofrontal cortex, physical and leisure activity, smoking

## 1 | INTRODUCTION

Lifestyle habits such as alcohol consumption, smoking, physical activity, and social integration are associated with structural and functional

connectivity differences in cortical brain regions such as the sensorimotor and prefrontal cortex (Bittner et al., 2019). Some lifestyle habits may pose serious risks to brain health, and others may be protective (Bittner et al., 2019), so it is important to understand better how lifestyle factors relate to brain function. This and other research described below was performed with moderate numbers of

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participants, but typically below 550. The aim of the present investigation is to investigate how a wider range of (7) lifestyle habits relate to brain structure and function using a much larger sample of approximately 20,000 individuals, to enable possible associations of different lifestyle habits with the structure and function of many brain regions to be measured. The overall aim is to facilitate better understanding of how different lifestyle habits relate to different brain regions with different functions. Use of this very large neuroimaging sample has the potential to reveal associations between lifestyle and brain systems that could not be previously revealed. Another feature of the present research was the use of the Human Connectome Project Multimodal Parcellation atlas (HCP-MMP), which defines 360 cortical regions based on cortical structure, functional connectivity, and activations in behavioral tasks (Glasser et al., 2016), with each cortical region having different connectivities and potentially functions (Rolls, Deco, et al., 2022a; Rolls, Deco, et al., 2023c; Rolls, Deco, et al., 2023d; Rolls, Deco, et al., 2022b; Rolls, Deco, et al., 2023e; Rolls, Wirth, et al., 2023g). This is the most detailed cortical atlas that we know in terms of providing many cortical regions each with potentially separate computational functions and with connectivity between the regions that has been analyzed. The potential importance of this research is that lifestyle choices are considered, and it is important to know how they relate to brain connectivity, for brain differences between individuals might influence these lifestyle choices, or the lifestyle choices might have consequences that affect brain function. Indeed, we show that these lifestyle choices are related to important factors such as mental health. Further details of previous research on the relation between some lifestyle habits and brain structure or function follow.

Alcohol use is associated with lower performance and associated brain activations in a simple motor task (Parks et al., 2010), lower gray matter (GM) volume in the frontal cortex (Zahr et al., 2011), and higher functional connectivity of the reward-related medial orbitofrontal and anterior cingulate cortex (Cheng et al., 2019). Smoking has been associated with lower volume of the prefrontal cortex, orbitofrontal cortex, and anterior cingulate gyrus (Wang et al., 2015), and differences in resting state functional connectivity have been described (Bi et al., 2017; Fedota & Stein, 2015; Sutherland & Stein, 2018; Yuan et al., 2016), including lower functional connectivity of the lateral orbitofrontal cortex and precuneus (Cheng et al., 2019). In addition, dietary habits have been described as modifiable risk factors for Alzheimer's disease (Croll et al., 2018; Kalmijn et al., 1997).

Physical exercise has been related to a decreased risk of dementia (Buchman et al., 2012; Grande et al., 2014; Huang, Li, et al., 2022; Krell-Roesch et al., 2018; Scarmeas et al., 2009), reduced physical activity may be one of the preclinical symptoms of dementia or Mild Cognitive Impairment, and physical exercise may slow the course of cognitive deficits (Cotman & Engesser-Cesar, 2002; Laurin et al., 2001). Exercise may improve human cognitive function and memory (Middleton et al., 2010; Tan et al., 2017; van Uffelen et al., 2008), and physically more active older adults show less of the brain volume reduction associated with aging (Erickson et al., 2014).

Social interaction has been associated with higher GM (James et al., 2012; Mortimer et al., 2012), and conversely social isolation is a risk factor for dementia and is associated with lower temporal, frontal, and hippocampal GM volume (Shen et al., 2022).

In relation to mental health, it has been noted that healthier lifestyles may be beneficial for mental health (Walsh, 2011). For example, exercise and the use of fish oils may help to reduce depression in high-risk young people; and diet and exercise may both be neuroprotective and lower the likelihood of ensuing cognitive decline and accompanying brain changes (Walsh, 2011).

Because a combination of lifestyles might together lead to greater differences in brain health, structure, and function (Bittner et al., 2019), in the present investigation we also measured the association between the seven lifestyle measures investigated here and brain function when all risk measures were combined in a sum risk score, as well as each considered separately.

## 2 | METHODS

### 2.1 | Participants

The data used for this investigation were selected from the September 2019 public data release from the UK Biobank which includes a wide range of phenotypic information, as well as biological samples, for more than 500,000 participants (Rusk, 2018). The UK Biobank sample used in the present analyses included 19,415 participants with imaging data, after quality controls and removing some participants without behavioral data (of whom 9573 [49.31%] were female; age range, 45–78 years). The UK Biobank received ethical approval from the research ethics committee (REC reference 11/NW/0382). The present analyses were conducted under UK Biobank application number 19542. Written informed consent was obtained from each subject by UK Biobank. The demographic characteristics of participants are summarized in Table 1.

### 2.2 | Imaging data collection and preprocessing

The multi-modal imaging was collected using a standard Siemens Skyra 3 T running VD13A SP4, with a standard Siemens 32-channel RF receive head coil. The resting-state functional brain imaging data used in this study from 19,415 participants were obtained and processed by the UK Biobank. The details of the image acquisition are provided at the UK Biobank website in the form of a protocol (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367>). All the quality checking and data preprocessing procedures were conducted by the UK Biobank and the details of the preprocessing are available on the UK Biobank website (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977>) and elsewhere (Miller et al., 2016). Briefly, data preprocessing was carried out using FSL (FMRIB Software Library) by the UK Biobank team with the procedures described in (Miller et al., 2016). The data preprocessing included correction for spatial and gradient

**TABLE 1** Demographic characteristics of the 19,415 UK Biobank participants.

| Characteristics   | No. (%)         |
|---|-----------------|
| Age, mean (SD), years   | 61.53 (7.24)    |
| Female  | 9573 (49.31%)   |
| BMI, mean (SD), kg/m <sup>2</sup>                                 | 26.25 (3.83)    |
| Townsend deprivation index, mean (SD), points                     | -2.09 (2.59)    |
| Education qualifications  |                 |
| College or University degree                                      | 9388 (48.35%)   |
| A levels/AS levels or equivalent                                  | 2541 (13.09%)   |
| O levels/GCSEs or equivalent                                      | 3640 (18.75%)   |
| CSEs or equivalent  | 764 (3.94%)     |
| NVQ or HND or HNC or equivalent                                   | 1087 (5.60%)    |
| Other professional qualifications, for example: nursing, teaching | 914 (4.71%)     |
| Alcohol consumption (field ID: 1568,1578,1598,1608, 5364)         |                 |
| Healthy   | 14,798 (76.22%) |
| Unhealthy   | 4617 (23.78%)   |
| Alcohol frequency (field ID: 1558)                                |                 |
| Healthy   | 15,050 (77.52%) |
| Unhealthy   | 4365 (22.48%)   |
| Smoking status (field ID: 20116)                                  |                 |
| Healthy   | 18,775 (96.70%) |
| Unhealthy   | 640 (3.30%)     |
| Diet (field ID: 1289, 1299, 1309, 1319)                           |                 |
| Healthy   | 17,112 (88.14%) |
| Unhealthy   | 2303 (11.86%)   |
| Physical activity (field ID: 6164)                                |                 |
| Healthy   | 17,613 (90.72%) |
| Unhealthy   | 1802 (9.28%)    |
| Mobile phone time (field ID: 1120)                                |                 |
| Healthy   | 16,161 (83.24%) |
| Unhealthy   | 3254 (16.76%)   |
| Leisure&social activity (field ID: 6160)                          |                 |
| Healthy   | 15,703 (80.57%) |
| Unhealthy   | 3787 (19.43%)   |
| Sum risk score, mean (SD), points                                 | 1.07 (1.07)     |

distortions and head motion, intensity normalization and bias field removal, registration to the T1 weighted structural image, transformation to 2 mm Montreal Neurological Institute (MNI) space, and the FIX artefact removal procedure (Navarro Schroder et al., 2015; Smith, et al., 2013). Finally, the head motion parameters were regressed out and structured artefacts were removed by ICA + FIX processing (Independent Component Analysis followed by FMRIB's ICA-based X-noiseifier [Griffanti et al., 2014; Salimi-Khorshidi et al., 2014]). The data preprocessing pipeline developed by FMRIB (Oxford University

Centre for Functional MRI of the Brain) used here has been widely used in resting state fMRI studies (Colclough et al., 2017; Navarro Schroder et al., 2015; Smith et al., 2015; Vidaurre et al., 2018).

## 2.3 | Construction of the whole-brain functional connectivity network

After the preprocessing, the cortex was parcellated into 360 regions defined in the HCP-MMP atlas (Glasser et al., 2016) using the HCPex version which can be applied to volumetric data and which adds 66 subcortical regions (Huang, Rolls, et al., 2022). The time series were extracted by determining the mean of the BOLD signals across all voxels within each region across 490 time points with TR = 0.735 s. The whole-brain functional network (360\*360 regions with 64,620 functional connectivity links) was established by calculating the Pearson correlation between the BOLD (blood oxygen level-dependent) signal for all pairs of brain regions for each individual participant, followed by z transformation to improve normality (Finn et al., 2015; Rosenberg et al., 2016). A list of these regions in the order defined in HCPex (Huang, Rolls, et al., 2022) and used here is provided in Table S1.

## 2.4 | Structural magnetic resonance imaging data

Quality-controlled T1-weighted neuroimaging data, and processed by the UK Biobank with FreeSurfer, were used in the current study (Littlejohns et al., 2020). Details of the imaging protocol can be found in an open-source document ([https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain\\_mri.pdf](https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf)). Neuroimaging data were collected with a standard Siemens Skyra 3 T scanner with a 32-channel head coil. T1 images were processed with FreeSurfer; surface templates were used to extract imaging-derived phenotypes referred to as atlas regions' surface area, volume, and mean cortical thickness (Desikan et al., 2006). Subcortical regions were extracted via FreeSurfer's aseg tool (Fischl et al., 2002). FreeSurfer Destrieux (a2009s) parcellation (Category ID 197) and aseg (Category ID 190) atlases corresponding to 148 cortical regions and 66 subcortical regions were used in this study (Destrieux et al., 2010). The Qoala-T approach was used to check FreeSurfer outputs, supplemented by manual checking of outputs close to the threshold. Any FreeSurfer outputs that failed to pass quality control were not included in the FreeSurfer imaging-derived phenotypes provided by the UK Biobank (Littlejohns et al., 2020).

## 2.5 | Healthy lifestyle phenotypes

The sum risk score of lifestyles applied in this study is a sum score for seven lifestyles for each of which the participants were split into two groups. The sum risk score means the risk level for a poor lifestyle,

with each lifestyle measure for an individual having a binary code, 0 or 1, with 1 the lifestyle that was more likely to be a risk to health. Seven lifestyle variables were used in this study to define the lifestyle risk score, and they were alcohol consumption, alcohol frequency, smoking status, diet, physical activity, mobile phone time, and leisure or social activity, with details provided next.

For alcohol consumption (measured by the sum of the average weekly intake of red wine, champagne plus white wine, beer plus cider, spirits and other alcoholic drinks, field IDs 1568,1578,1598,1608, and 5364), a weekly alcohol intake of more than 14 glasses resulted in a score of 1 (Chudasama et al., 2020).

For alcohol frequency, Field 1558, the participants were asked, "About how often do you drink alcohol?", and ranked as 1, Daily or almost daily; 2, Three or four times a week; 3, Once or twice a week; 4, One to three times a month; 5, Special occasions only; 6, Never. Participants who answered "1, Daily or almost daily" received a score of 1 for this lifestyle measure.

For smoking, Field 20,116, a score of 0 was given if not a current smoker, and 1 if a current smoker (Bittner et al., 2019).

For diet, an individual was scored as 1 if the sum intake for cooked vegetables (field id: 1289), salad/raw vegetable (field id:1299), fresh fruit (field id:1309) and dried fruit (field id: 1319), was less than 5 pieces per day (Chudasama et al., 2020).

For physical activity, field 6164, participants with less than 500 MET-minutes/week were scored 1 as reflecting a low amount of physical activity (<https://www.nhs.uk/live-well/exercise/>) (Bittner et al., 2019). (The intensity for this measure was the standardized metabolic equivalent of the task (MET) value (Ainsworth et al., 2000)).

For mobile phone time, field 1120 asked, "Over the last 3 months, on average how much time per week did you spend making or receiving calls on a mobile phone?". The data were split into half, with those with  $\leq 1$  h/week over the last 3 months given a score for low mobile phone use 1, as low mobile phone use in this age group might indicate potential problems.

For leisure or social activity, field 6160 asked "Which of the following do you attend once a week or more often? (You can select more than one)". Participants with  $< 1$  activities were scored as 1 for a low amount of leisure or social activity (Bittner et al., 2019).

When analyses were performed for the associations between brain function and structure and each lifestyle considered separately, the correlations were measured using the full range of data available for each lifestyle, for example, the amount of physical activity in MET-min/week, using the same type of general linear model (GLM) described next.

In terms of age differences across this population of  $N = 19,415$  individuals, almost no correlation between the combined lifestyle score and age was found, with  $r = .02$ ,  $p = .004$ ,  $N = 19,415$  individuals in the age range 45–78, and regressing out gender, BMI, educational qualification, and Townsend index. A correlation of  $r = -.21$  was found between mobile phone use and age, reflecting less mobile phone use in the higher part of the age range.

## 2.6 | Measurements of associations between the sum risk lifestyle score and brain structure and functional connectivity

A GLM was used to test the association of the sum risk lifestyle score with each of the brain measures: functional connectivity which we measured; and cortical volume and subcortical volume provided by the UK Biobank. The independent variable was the sum score of risk from the seven binary lifestyle variables (providing a score of 0–7 for each participant). The dependent variables were the functional connectivity links, and the covariates to be regressed out of the analysis were gender, age, body mass index (BMI), Townsend deprivation index (which includes information for example about the loss of parents), educational qualifications, head motion (mean Framewise Displacement), and the imaging collection site (coded as 3-column dummy variables as provided by the UK Biobank, noted as 11,025, 11,026, 11,027, and 11,028). In this analysis, 37,286 participants had neuroimaging data, and after quality control and missing data were deleted, 19,415 participants were involved. Bonferroni correction was used to correct for multiple comparisons across all functional connectivity links in the  $360 \times 360$  functional connectivity matrix. The analysis was also performed for each of the lifestyle measures separately using their full continuous values where possible, to assess possible differences in brain regions related to each measure.

Similarly, we used a GLM to test the association of the risk score with the cortical brain thickness based on the Destrieux Atlas (Destrieux et al., 2010; Fischl et al., 2004), and separately with the ASEG (Fischl et al., 2002) subcortical brain volume. The variables mentioned above were used as nuisance covariates of no interest except head motion. Bonferroni correction ( $p < .05$ ) was used in subcortical volume analysis for multiple comparisons. FDR correction ( $p < .05$ ) was used in cortical thickness analysis for multiple comparisons.

## 2.7 | Association analysis of the sum risk score and mental health problems

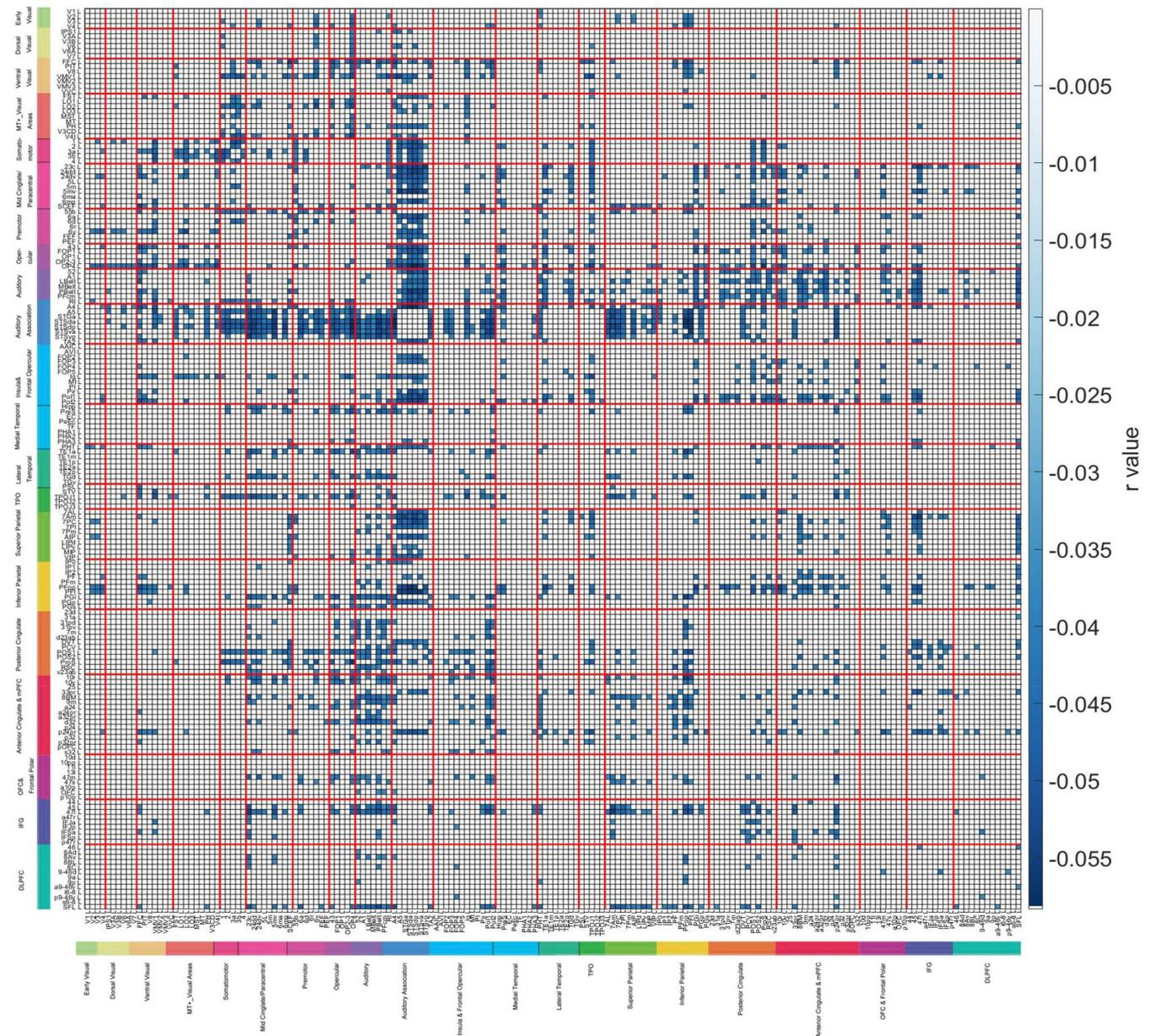
The correlations between the sum risk score and mental health problems were measured to examine whether the sum risk score is associated with mental health problems. Specifically, a partial Spearman correlation between mental health problems scores and the sum risk lifestyle score with age, gender, body mass index, education, and Townsend social deprivation index regressed out was calculated. The mental health problems scores consisted of nine measures, for: addiction, anxiety, depression, mania, mental distress, unusual and psychotic experiences, self-harm, trauma, and wellbeing. These categories are specified under the mental health tab of the online questionnaires in the UK Biobank dataset (<https://biobank.ctsu.ox.ac.uk/crystal/label.cgi?id=136>). For each category, a mean score of all the questions was calculated as an overall score. Similarly, to investigate the association between functional connectivity each lifestyle factor separately, partial Spearman correlation analysis was used, after removing the seven confounding variables: age, gender, BMI, qualification of education, Townsend index, imaging collection site and head motion, with  $N = 19,415$ . All  $r$  values in the Figures are Spearman correlations.

### 3 | RESULTS

#### 3.1 | Combined lifestyle risk and brain function

We first measured whether the combined lifestyle risk score was correlated with any of the functional connectivities, to obtain some evidence on how large and extensive the set of connectivities might be that were correlated with poor lifestyle. Figure 1 shows that many functional connectivities were negatively correlated with a

poor combined lifestyle score. A total of 5343 links were significant after Bonferroni correction for  $p < .05$  (which corresponds to uncorrected  $p = 7.7 \text{ e-}07$ ), and the analysis involved 19,415 participants. Details of the most significant 50 links are shown in Table S3. One set of brain regions with negative correlations with the combined risk score involved somatosensory and motor cortical regions in the Somato-motor, Opercular cortical divisions, and including also regions 6v (premotor), insular lg, Po1 and Po2, and inferior parietal PFop and PFT. (Descriptions of these regions and their connectivity



**FIGURE 1** The association between the sum risk score of lifestyles (the sum risk level for a potentially poor lifestyle, including high alcohol consumption, high alcohol frequency, smoking, poor diet, low physical activity, low mobile phone time, and low leisure/social activity) and functional connectivities in the left hemisphere. 5343 links were significant after Bonferroni correction for  $p < .05$  (which corresponds to uncorrected  $p = 7.7 \text{ e-}07$ ), and the analysis involved 19,415 participants. Negative  $r$  values (blue) indicate that a high risk lifestyle score is associated with lower functional connectivity. ( $N = 19,415$  participants.) A list of the abbreviations of the brain regions, and their cortical Division indicated by the different color labels, is provided in Table S1. The red lines separate the cortical Divisions in the Human Connectome Project HCP-MMP atlas [see Table S1; (Glasser et al., 2016; Huang, Rolls, et al., 2022)].

are provided by Rolls, Deco, et al. (2023d).) A second set of regions with negatively correlated functional connectivities were in the auditory association division, which includes auditory regions A4, A5 and RI, and cortical regions in the superior temporal sulcus (STS) that are involved in semantic representations for language (Rolls, Deco, et al., 2022a; Rolls, Rauschecker, et al., 2023f). Other connected language regions (Rolls, Deco, et al., 2022a; Rolls, Rauschecker, et al., 2023f) also had negatively correlated functional connectivities, including temporal pole TGd, temporo-parietal junction TPOJ1, parts of Broca's area 45 and 47l with the connected premotor 55b, and the superior frontal language area (SFL). A third set of regions with connectivities negatively correlated with the combined lifestyle risk score involved the hippocampal memory system and some connected posterior cingulate cortex regions. The regions involved included the Hippocampus, Presubiculum, POS1, and ProS which is where the retrosplenial scene area is located (Rolls, Deco, et al., 2023c; Rolls, Deco, et al., 2022b; Rolls, Wirth, et al., 2023g; Sulpizio et al., 2020).

It was found that the lifestyle measures used were not highly correlated with each other, as shown in Table S2, with the highest correlations found between physical activity and leisure activity ( $r = .20$ ); and alcohol consumption and smoking status (0.20), and so we next analyzed how each lifestyle measure taken separately might be correlated with the functional connectivities.

## 3.2 | Functional connectivities associated with the separate lifestyle risk factors

### 3.2.1 | Physical activity

It is shown by blue in Figure 2 that a low physical activity was correlated with low functional connectivities between some cortical regions. The 30 most significant links are shown in Table S4. One set of brain regions with negative correlations with the low physical activity involved somatosensory and motor cortical regions similar to those in the combined analysis in Figure 1. A second set of regions with negatively correlated functional connectivities were the auditory and language related regions also described for the combined lifestyle score in Figure 1. A third set of regions with low connectivities associated with low functional connectivities involved the hippocampal memory system and some connected posterior cingulate cortex regions also described for the combined lifestyle score in Figure 1. The functional connectivity correlation matrices for the combined risk score and physical activity were somewhat similar ( $r = 0.60$ ,  $p < 10^{-15}$ ,  $N = 19,415$ ).

### 3.2.2 | Leisure/social activity

It is shown by blue in Figure 3 that a low leisure/social activity was correlated with low functional connectivities between some cortical regions. The 30 most significant links are shown in Table S5. The

three sets of cortical regions involved were similar to those for the combined lifestyle (Figure 1) and physical activity (Figure 2) measures, though perhaps the hippocampal involvement was lower.

### 3.2.3 | Mobile phone time

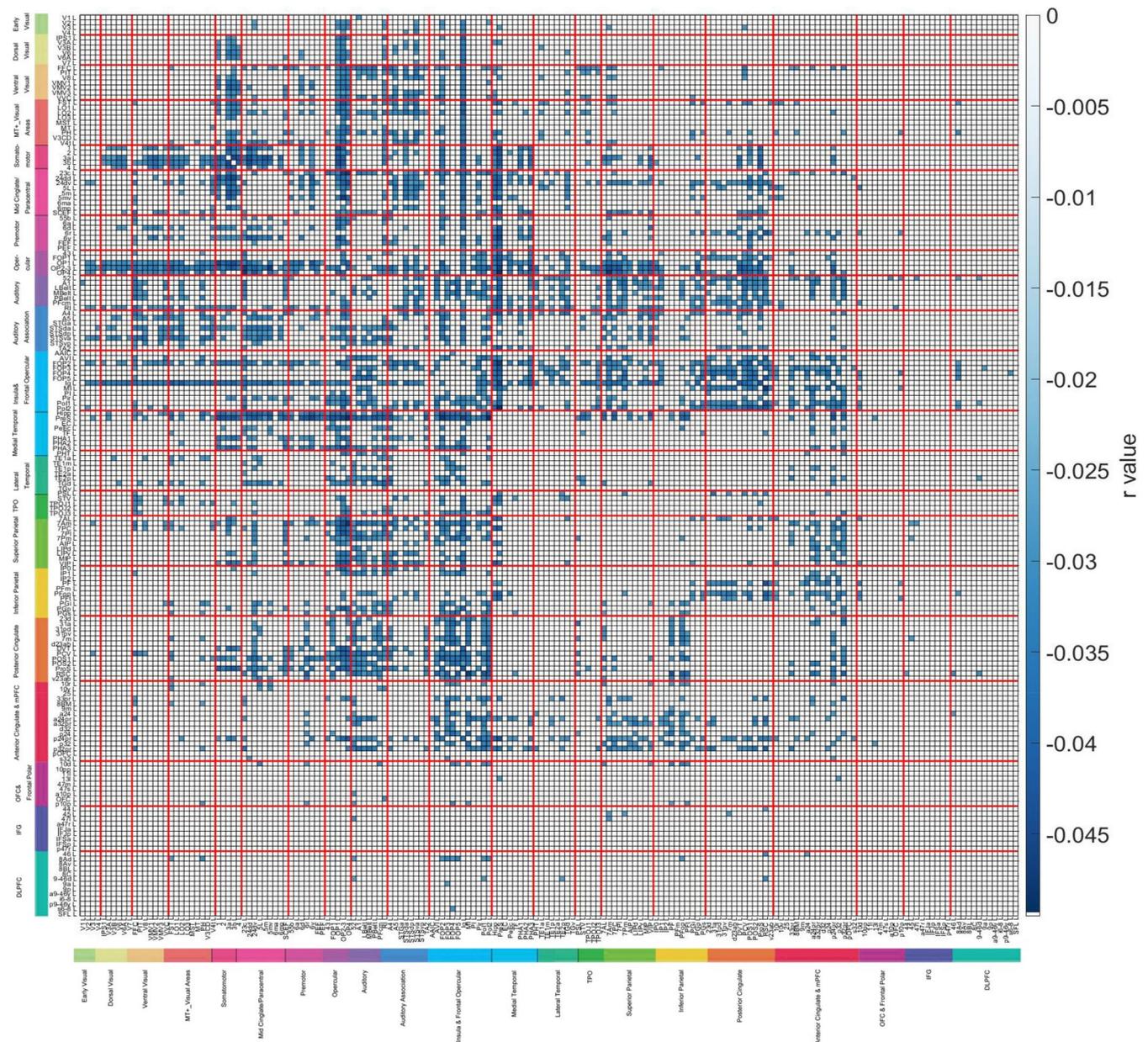
It is shown by blue in Figure 4 that a low mobile phone time use was correlated with low functional connectivities between some cortical regions. The 30 most significant links are shown in Table S5. Low mobile phone time was associated with lower somatosensory-motor functional connectivities, but for phone time, the low functional connectivities were much more with the auditory and language-related regions, especially the STS regions, the language-related superior temporal visual (STV) region as well as TPOJ1 (Figure 4). The emphasis on low auditory and language-related functional connectivities could easily be related to the low mobile phone use, though which is causative in this relation is not known. For mobile phone use, the hippocampal system was less involved than for the combined score, and for physical activity and leisure/social activity. In addition to these generally lower functional connectivities of STS auditory association/language related regions, low mobile phone use was correlated with higher functional connectivities (red in Figure 4) for some regions, including STS language-related regions with inferior parietal PFM, posterior cingulate 31pv and d23ab, anterior cingulate p24, a24 and 9m, and parts of the prefrontal cortex. Low mobile phone use could have contributed to the negative correlations found in the combined lifestyle risk analysis shown in Figure 1.

### 3.2.4 | Alcohol consumption

It is shown by blue in Figure S2 that a higher alcohol consumption is associated with lower functional connectivities between some cortical regions. The 30 most significant links are shown in Table S6. These regions include especially auditory and language-related STS regions (see Rolls, Deco, et al., 2022a; Rolls, Rauschecker, et al., 2023f), including their links with each other and with other cortical regions. The regions with functional connectivities positively correlated with alcohol consumption included links involving 10v in the ventromedial prefrontal cortex and subgenual area 25 (Rolls, Deco, et al., 2023e). These positive correlations with alcohol consumption are consistent with an earlier investigation in much younger participants generally less than 25 years old (Cheng et al., 2019). The negative correlations were less evident in this earlier investigation, and that may be an age-related difference, in that the participants in the present investigations were mostly above 55 years of age.

### 3.2.5 | Alcohol frequency

For alcohol frequency, as Figure S3 shows (see also Table S7), higher functional connectivity associated with higher alcohol frequency was found for orbitofrontal cortex 13l, ventromedial 10r, some posterior



**FIGURE 2** Low physical activity is associated with low functional connectivities (blue). The correlation (*r* values) between low physical activity (potentially a lifestyle risk factor) and functional connectivities in the left hemisphere. The physical activity measure is the total weekly leisure-time physical activity (MET-minutes/week). The matrix shows the 7256 significant links after Bonferroni correction (Bonferroni corrected,  $p < .05$ ;  $p = 7.7 \text{ e-}07$ ) in the left hemisphere. The covariates described in the Methods were regressed out. ( $N = 19,415$ ).

cingulate cortex regions, and some other regions. Lower functional connectivity associated with higher alcohol frequency was found especially for FOP2 and FOP3, frontal opercular areas probably associated with oral somatosensation and perhaps taste (Rolls, Deco, et al., 2023d; Rolls, Deco, et al., 2023e).

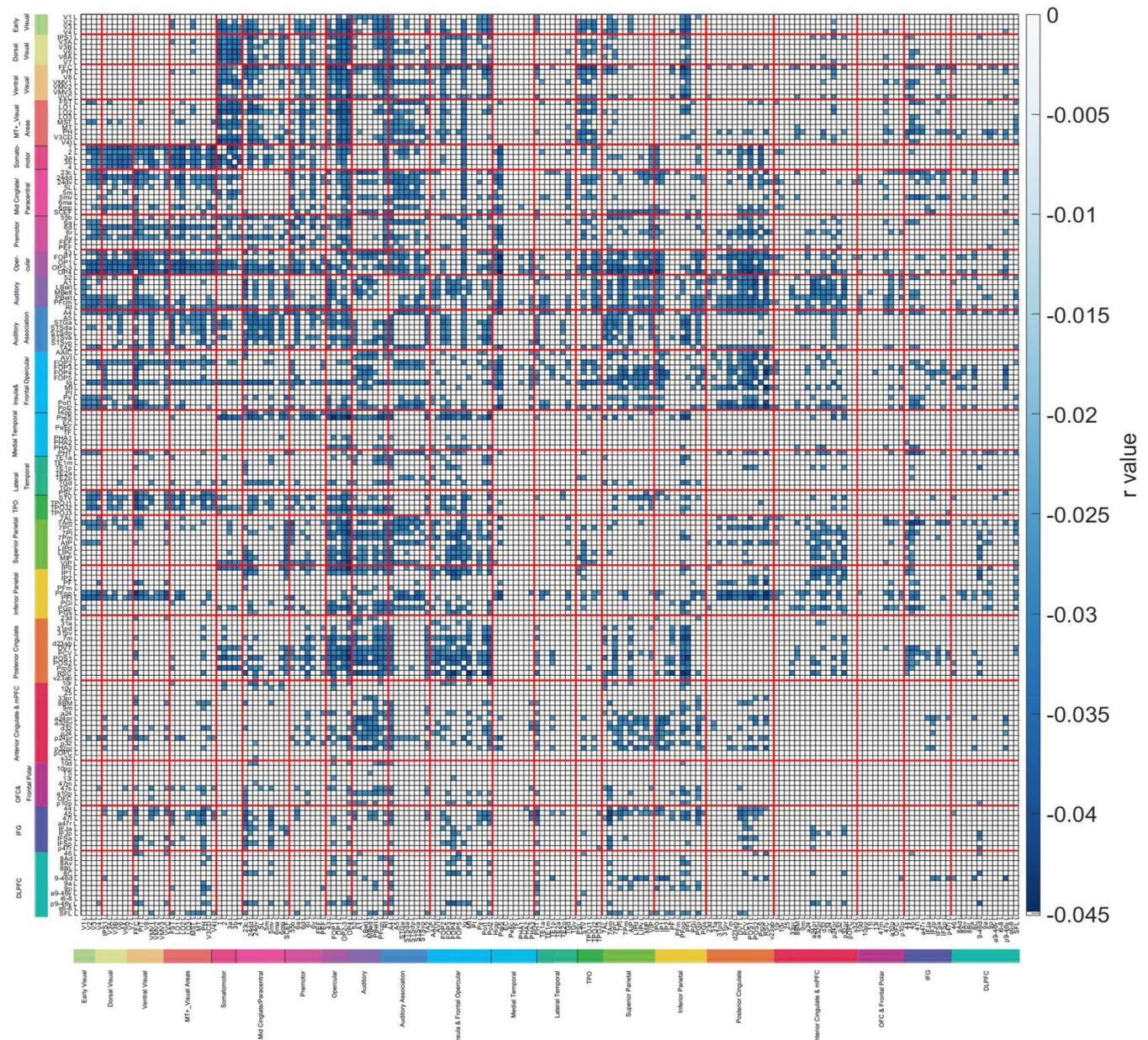
### 3.2.6 | Smoking status

For smoking status, as shown in Figure S4 (see also Table S8), all the significantly associated links (905) are negatively associated with smoking status; that is, smokers have lower functional connectivities of the significant regions. A cluster of links involve connectivity

between auditory cortex regions and prefrontal cortex area 8, which is implicated in top-down attention (Rolls, Deco, et al., 2023d). The link with attention is of interest, as nicotine probably acts to enhance attention. Lower functional connectivities in smokers have been described before, though in younger smokers (Cheng et al., 2019).

### 3.2.7 | Diet

For diet (intake of vegetables and fruit per week), as shown in Figure S5 (see also Table S9), a poor diet (low on vegetables and fruit) is associated with low functional connectivity of links involving especially FOP5 (where the primary taste cortex is located (Rolls, Deco,



**FIGURE 3** The association between a low value for leisure/social activity and functional connectivities. (Leisure/social activity was measured by the number of such activities of each participant.) The matrix shows the 9223 significant links after Bonferroni correction (Bonferroni corrected,  $p < .05$ ;  $p = 7.7 \text{ e-}07$ ) in the left hemisphere and their  $r$  value. Negative  $r$  values indicate that low leisure/social activity, considered as a possible lifestyle risk factor, is associated with a low functional connectivity. ( $N = 19,415$ ).

et al., 2023d) and the insula (Ig) which has somatosensory representations (Rolls, Deco, et al., 2023d). a32 and DVT also have some similar correlations.

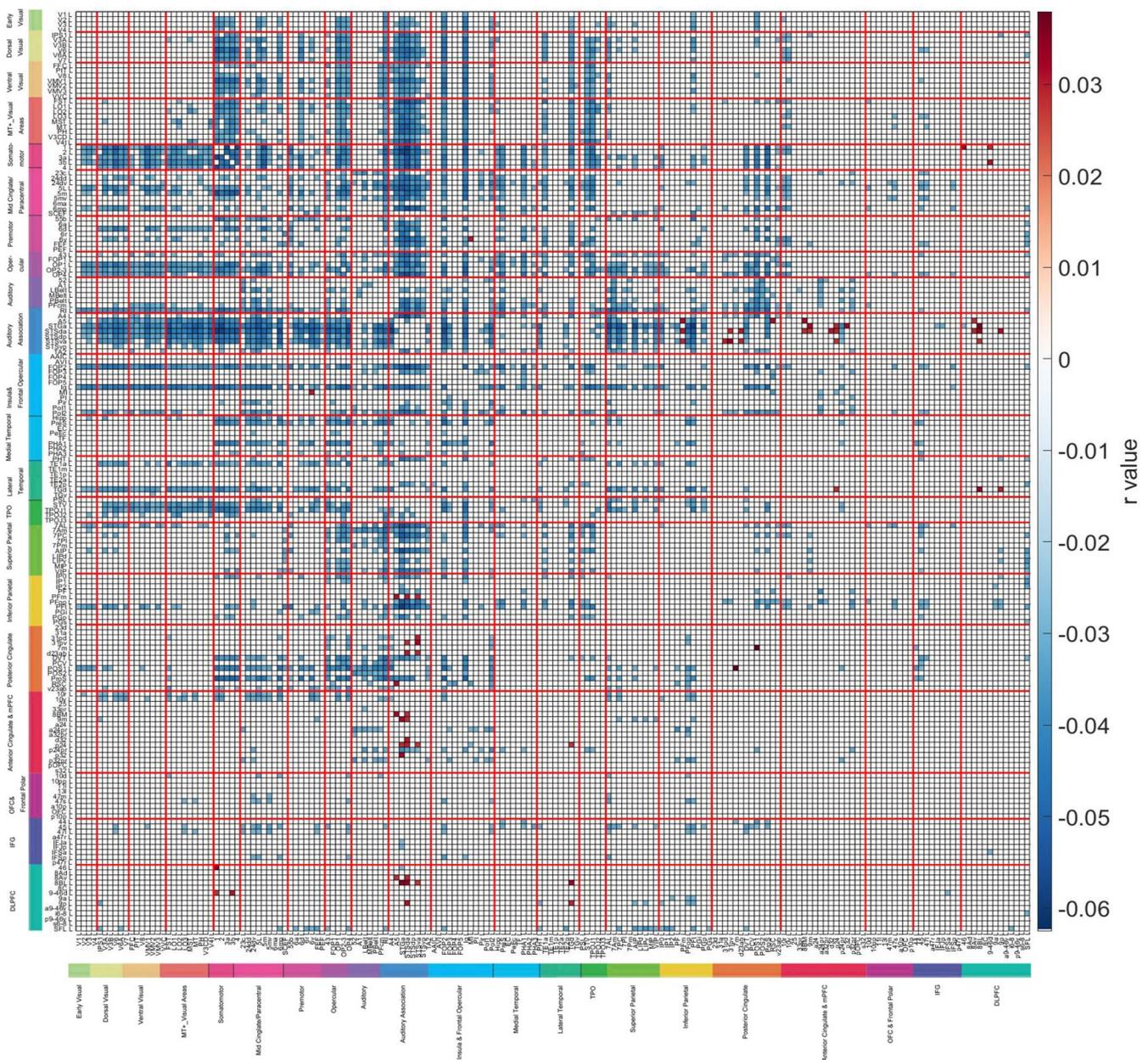
### 3.3 | Combined lifestyle risk and mental health

In order to assess the relevance of the combined lifestyle risk score to human behavior, the correlation was measured between the combined sum risk score and the measures of mental health problems available in the UK Biobank from the individuals who had been neuroimaged. As shown in Table 2, all the mental health problems were

positively correlated with the sum risk score, and well-being was negatively correlated ( $r = -.09$ ,  $p = 1.59 \text{ e-}31$ ,  $N = 17,599$ ). The sum risk score was also associated with addiction at  $r = .09$  ( $p = 2.97 \text{ e-}35$ ,  $N = 17,391$ ), and with self-harm at  $r = .05$  ( $p = 8.60 \text{ e-}13$ ,  $N = 17,597$ ). (Bonferroni correction for multiple comparisons required significance at  $p < 5.6 \text{ e-}02$ ).

### 3.4 | Combined lifestyle risk and cortical thickness

In addition, we also investigated the relationship between the combined lifestyle risk score and the cortical thickness based on the



**FIGURE 4** Low mobile phone use is associated with low functional connectivities (blue) in some brain systems. The matrix shows the 8151 significant links after Bonferroni correction (Bonferroni corrected,  $p < .05$ ;  $p = 7.7 \text{ e-}07$ ) in the left hemisphere with the  $r$  value. Mobile phone time was measured in hours per week. Negative  $r$  values (blue) indicate that low mobile phone use is associated with low functional connectivity. ( $N = 19,415$ )

Destrieux Atlas from the UK Biobank preprocessing ( $N = 21, 217$ ). In participants with a higher risk score, the cortical thickness was lower in the cortex in the STS, angular gyrus, the marginal branch of the cingulate sulcus, the paracentral gyrus, the precentral gyrus, and the superior frontal gyrus etc. (Bonferroni corrected,  $p < .05$ , Figure 5).

### 3.5 | Combined lifestyle risk and subcortical volume

As Figure 6 shows, the thalamic and the pallidal volume were significantly negatively associated with the combined lifestyle risk score

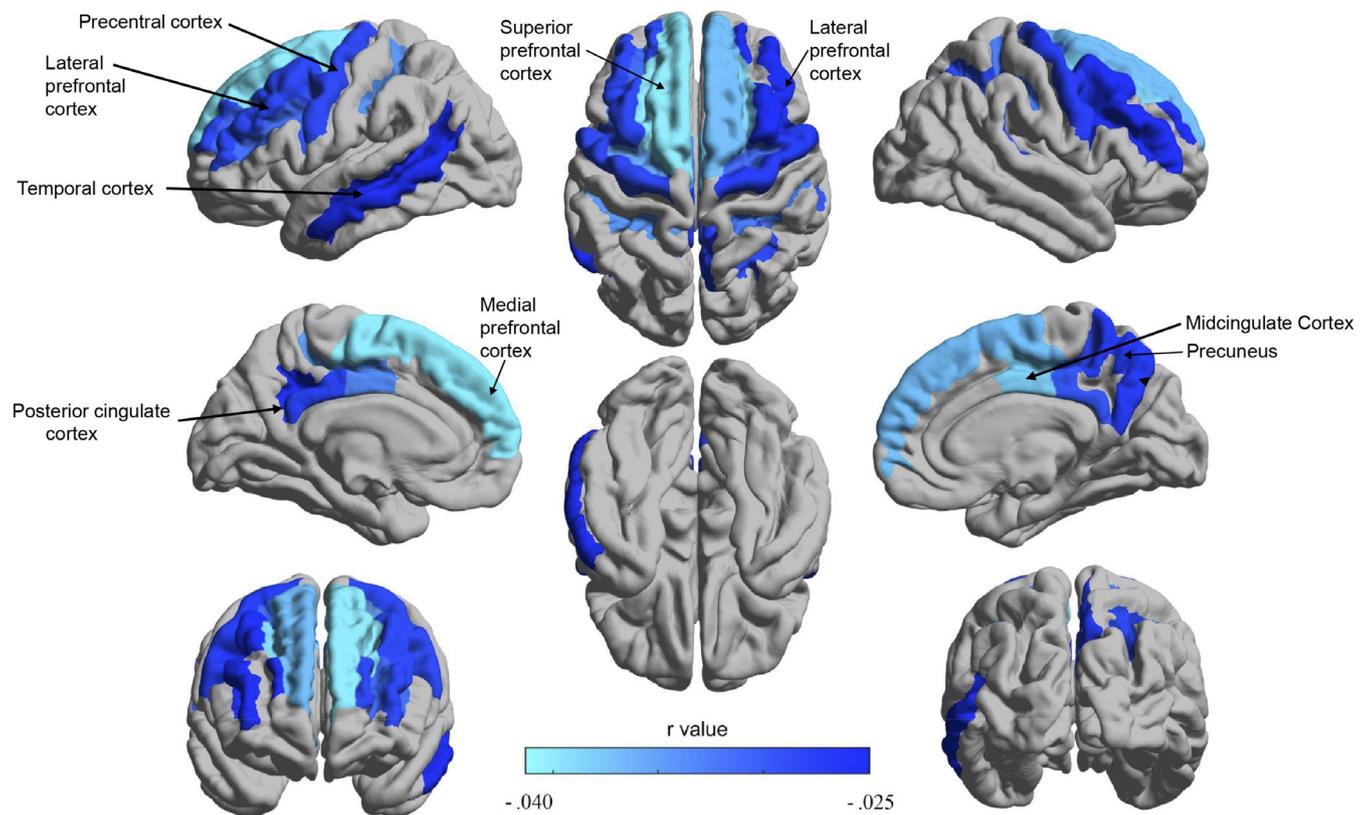
(bilaterally). In addition, smaller volume in the left amygdala and the right hippocampus was significant after FDR correction at  $p < .05$  ( $p = 2.94 \text{ e-}02$ ,  $N = 21,201$ ). In addition, the volume of the ventricle was larger in participants with a higher sum risk score. For the left ventricle volume ( $r = .034$ ,  $p = 1.04 \text{ e-}06$ ,  $N = 21,201$ ), and for the right ventricle volume ( $r = .032$ ,  $p = 3.14 \text{ e-}06$ ,  $N = 21,201$ ).

## 4 | DISCUSSION

First, it was shown that for the sum of a wide range of what might be poor lifestyle variables, high alcohol consumption, high alcohol

**TABLE 2** The association between the sum risk score and mental health scores.

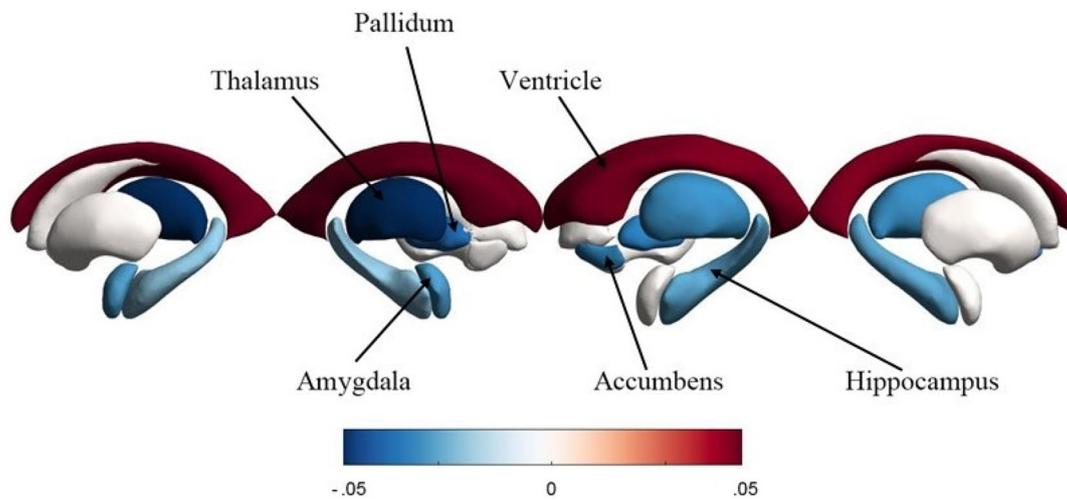
|   | Addiction | Anxiety   | Depression | Mania     | Mental distress | Psychotic experience | Self-harm | Trauma    | Well-being |
|---|-----------|-----------|------------|-----------|-----------------|----------------------|-----------|-----------|------------|
| r | .09       | .04       | .04        | .04       | .04             | .01                  | .05       | .02       | -.09       |
| p | 2.97 E-35 | 4.64 E-07 | 8.18 E-07  | 4.29 E-09 | 2.14 E-06       | 1.36 E-01            | 8.60 E-13 | 5.65 E-03 | 1.59 E-31  |
| N | 17,391    | 17,602    | 17,603     | 17,542    | 17,600          | 17,598               | 17,597    | 17,603    | 17,599     |



**FIGURE 5** Brain regions with their cortical thickness significantly associated with the sum risk score (the sum risk level for a poor lifestyle, including alcohol consumption, alcohol frequency, smoking status, diet, physical activity, mobile phone time, and leisure or social activity) (Bonferroni corrected,  $p < .05$ ). The blue color indicates brain regions with low cortical thickness associated with a higher risk score. ( $N = 21,217$ ).

frequency, smoking, poor diet, low physical activity, and low mobile phone time, many cortical functional connectivities were lower, and they especially included connectivities of cortical regions in the STS, the somatosensory/motor cortical regions, and the hippocampal system (Figure 1). When analyzed separately, low physical activity (Figure 2), and low social/leisure activity (Figure 3) were especially associated with low functional connectivities of somatosensory/motor cortical regions. Low mobile phone use was associated with low functional connectivities especially of cortical regions in the STS known to be involved in social, face and language processing (Pitcher & Ungerleider, 2021; Rolls, Deco, et al., 2023c; Yokoyama et al., 2021) and in semantic representations for language (Rolls, Deco, et al., 2022a), with also involvement of somatosensory/motor cortical regions (Figure 4). (Low mobile phone time might perhaps reflect lack of communication with social contacts, and low leisure/social activity). High alcohol consumption was associated with high functional

connectivities that included links involving 10v in the ventromedial prefrontal cortex and subgenual area 25 (Rolls, Deco, et al., 2023e), and with low functional connectivities of auditory cortical regions (Figure S2). For smoking, lower functional connectivity was found for links involving auditory cortex regions and prefrontal cortex area 8 (Figure S4), which is implicated in top-down attention (Rolls, Deco, et al., 2023d). Poor diet (at least as assessed by a low consumption of vegetables and fruit) was associated with low functional connectivity of links involving especially FOP5 (where the primary taste cortex is located (Rolls, Deco, et al., 2023d)) and the insula (I<sub>g</sub>) which has somatosensory representations (Rolls, Deco, et al., 2023d) (Figure S5). The combined risk score was also associated with low cortical thickness in some regions (including the cortex in the STS precentral and paracentral regions, parietal regions, and the superior frontal gyrus), and lower volumes of the globus pallidus, hippocampus, and amygdala. The combined risk score was associated with problems in life,



**FIGURE 6** Brain regions with their subcortical volume significantly associated with the sum risk score (the sum risk level for a poor lifestyle, including alcohol consumption, alcohol frequency, smoking status, diet, physical activity, mobile phone time and leisure or social activity) (FDR corrected,  $p < .05$ ). The blue color indicates brain regions with low volume negatively associated with higher risk score. ( $N = 21,201$ ) The color bar shows the  $r$  value.

including mental health problems, addiction, and self-harm. The results described here update previous research with a much lower sample size (549 participants) in which some higher functional connectivities were associated with combined lifestyle risks (Bittner et al., 2019), whereas here with a much larger sample size of 19,415 participants, many functional connectivities were highly significantly negatively correlated with lifestyle risks (Figure 1). An additional difference was that this previous study measured only some functional connectivities using a seed-based approach, and here we used an unbiased whole-brain approach in which the functional connectivities between all 360 cortical regions were analyzed (Figure 1).

The findings described here are associations, and do not test whether the lifestyle differences cause the brain differences, or vice versa. However, it could be that some of these lifestyle factors are caused by brain differences, with for example smoking perhaps being performed in part to increase cortical arousal against a background of lower functional connectivities, and drinking being performed in part due to higher connectivity of some reward-related brain regions such as the ventromedial prefrontal cortex (Cheng et al., 2019). For the low physical activity and leisure/social lifestyle measures, the differences in cortical connectivity of somatosensory-motor regions might be at least in part an effect of the difference in the lifestyle. Where physical activity may relate to reduced cerebral blood flow, there could be consequences for impaired cognitive function, including the memory-related functions of the hippocampus (Rolls, 2022). One point that the findings described here do emphasize is that the brains of different individuals can have quite different connectivity, which can be related to their behavior, and in the present case to their lifestyle. In this context, it would be of interest to investigate in a longitudinal design the associations between lifestyle choices and brain function. It would also be of interest to extend the findings to other populations, although we do note that this was a large sample of 19,415 individuals with neuroimaging data with a wide age range of 45–78 in the UK Biobank, as shown in Table 1.

The lower functional connectivity of regions in and related to the STS regions (FFC, STGa, STS dorsal anterior STSda, STS dorsal posterior STSdp, STS ventral anterior STSva, STS ventral posterior STSvp) is of regions involved in face expression encoding and social function (Freiwald, 2020; Hasselmo, Rolls, & Baylis, 1989; Hasselmo, Rolls, Baylis, & Nalwa, 1989; Pitcher & Ungerleider, 2021; Rolls, Deco, et al., 2023c; Yokoyama et al., 2021). The fusiform face complex (FFC) is a part of the ventral cortical stream that is specialized for computing by similar feature arrangement processes (Caffarra et al., 2021; Dehaene et al., 2005; Dehaene & Cohen, 2011; Perrett et al., 1982; Rolls, 2021b; Yeatman & White, 2021) as those involved in object recognition (Rolls, 2016a; Rolls, 2021a; Rolls, 2021b).

The lower functional connectivity related to poor lifestyle includes memory related regions such as the posterior cingulate cortex, the hippocampus (Hipp) and the presubiculum (PreS) (Ma et al., 2022; Rolls, Deco, et al., 2022b; Rolls, Wirth, et al., 2023g). The posterior cingulate HCP atlas division cortex (which includes 23d, 31a, 31pd, 31pv, 7m, d23ab, DVT, PCV, POS1, POS2, ProS, RSC, v23ab) is a key area region in which the posterior regions are related to memory (Bubb et al., 2017; Rolls, Wirth, et al., 2023g). The posterior cingulate cortex is consistently engaged by a range of tasks that examine episodic memory, including autobiographical memory, imagining the future, and spatial navigation and scene processing (Auger & Maguire, 2013; Leech & Sharp, 2014), and it provides connections to and receives connections from the hippocampal system (Rolls, Deco, et al., 2022b; Rolls, Wirth, et al., 2023g). As these participants were drawn from a general population without memory decline relating to dementia or any neurodegenerative disease, an implication is that the poor lifestyle may be associated with memory problems that have not been detected in individuals.

It was discovered in this investigation that a poor diet, low in vegetable and fruit, is associated with low functional connectivity of links involving especially FOP5 (where the primary taste cortex is located (Rolls, Deco, et al., 2023d)) and the insula (Ig) which has

somatosensory representations (Rolls, Deco, et al., 2023d) (Figure S5). The taste and oral texture sensory properties of food that are represented in these brain regions are important factors in the control of food intake (Rolls, 2016b; Rolls, 2016c; Rolls et al., 2015), and it would be very interesting to know whether differences in diet cause or are caused by these differences in functional connectivity of taste and oral somatosensory cortical regions. In addition, lower functional connectivity associated with higher alcohol frequency was found especially for FOP2 and FOP3 (Figure S3), frontal opercular areas probably associated with oral somatosensation and perhaps taste (Rolls, Deco, et al., 2023d; Rolls, et al., 2023e), raising similar questions about the role of oral sensation in alcohol use.

In conclusion, the findings described here have produced substantial advances in our understanding of how different lifestyle risks are related to differences of the connectivity of different brain regions, with highlights as follows. First, we used a much larger sample of participants, 19,415, than in most earlier studies (Bi et al., 2017; Bittner et al., 2019; Fedota & Stein, 2015; Sutherland & Stein, 2018; Yuan et al., 2016), and this enables the findings to be more robust than in studies with fewer participants, in the context that the connectivity of many cortical regions is necessary to understand which systems are related to different lifestyle choices. Second, we used the HCP-MMP cortical atlas (Glasser et al., 2016; Huang, Rolls, et al., 2022) in which 360 cortical regions are defined, and a feature of this atlas is that it defines a large number of different cortical regions each with potentially different functions and connectivity, because it is based on cortical structure (myelin content and thickness), on functional connectivity, and on task-related fMRI. A feature of this atlas is that many of the cortical regions can be related to corresponding regions in macaques, which helps complementary neurophysiological investigations to be brought to bear when considering function, as illustrated above. Another feature of this atlas is that the effective connectivity of all 360 cortical regions is starting to be understood, which helps greatly with understanding function (Rolls et al., 2022a; Rolls, et al., 2023a; Rolls, et al., 2023b; Rolls, et al., 2023c; Rolls, et al., 2023d; Rolls, et al., 2022b; Rolls, et al., 2023e; Rolls, et al., 2023f; Rolls, et al., 2023g). A third highlight is that because this HCP-MMP atlas (Glasser et al., 2016; Huang, Rolls, et al., 2022) was used, it is possible to consider how the functions of the different cortical areas are related to the different lifestyle choices, helping to elucidate why those lifestyle choices may be made and/or the implications of those lifestyle choices for brain function, as shown above in the Discussion and thereby going beyond a previous investigation (Bittner et al., 2019). A fourth highlight is that we tried analysis of the association of a combination of lifestyle choices with brain connectivity and function following a previous approach (Bittner et al., 2019), but found that it was also important to analyse the association with each lifestyle choice separately, because each lifestyle choice is associated with different cortical connectivities, as we show. Finally, we note that this may be one of the largest association studies between functional connectivity and measures of behavior yet performed, with a  $360 \times 360$  functional connectivity matrix between cortical regions, and 19,415 participants used to help robustly analyse differences of behavioral associations with these functional connectivities.

## AUTHOR CONTRIBUTIONS

**Ruiqing Feng:** Investigation, data curation, formal analysis, methodology, software, writing—original draft, writing—review & editing. **Edmund T. Rolls:** Conceptualization, investigation, methodology, supervision, validation, writing—original draft, writing—review & editing. **Jianfeng Feng:** Conceptualization, funding acquisition. Prof Feng and Ruiqing Feng verified the underlying data. All authors read and approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

## DATA AVAILABILITY STATEMENT

The data analyzed are available from the UK Biobank (<https://biobank.ctsu.ox.ac.uk>). The UK Biobank obtained the ethics permission for their data collection. The code used standard Matlab functions.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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