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Estimations of the weather effects on brain functions using functional MRI – a cautionary tale

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Abstract

The influences of environmental factors such as weather on human brain are still largely unknown. A few neuroimaging studies have demonstrated seasonal effects, but were limited by their cross-sectional design or sample sizes. Most importantly, the stability of MRI scanner hasn't been taken into account, which may also be affected by environments. In the current study, we analyzed longitudinal resting-state functional MRI (fMRI) data from eight individuals, where the participants were scanned over months to years. We applied machine learning regression to use different resting-state parameters, including amplitude of low-frequency fluctuations (ALFF), regional homogeneity (ReHo), and functional connectivity matrix, to predict different weather and environmental parameters. For a careful control, the raw EPI and the anatomical images were also used in the prediction analysis. We first found that daylight length and temperatures could be reliability predicted using cross-validation using resting-state parameters. However, similar prediction accuracies could also achieved by using one frame of EPI image, and even higher accuracies could be achieved by using segmented or even the raw anatomical images. Finally, we verified that the signals outside of the brain in the anatomical images and signals in phantom scans could also achieve higher prediction accuracies, suggesting that the predictability may be due to the baseline signals of the MRI scanner. After all, we did not identify detectable influences of weather on brain functions other than the influences on the stability of MRI scanners. The results highlight the difficulty of studying long term effects on brain using MRI.

Keywords: daylight length, environmental effects on brain, machine learning regression, resting-state, scanner stability, temperature, weather.

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1. Introduction

Daily environmental factors such as weather and seasonality affect mood and cognitive functions (Keller et al. 2005; Denissen et al. 2008; Cedeño Laurent et al. 2018; IJzerman et al. 2018; Lim et al. 2018), and may lead to pathological affective disorder (Kurlansik and Ibay 2012). The effects on individuals may be small, but the collective effects may lead to broader impacts, e.g. on stock markets (Saunders 1993; Hirshleifer and Shumway 2003). To better understand the effects of weather and seasonality on mood or cognitions, it is critical to study their effects on brain functions. A few human neuroimaging studies have explored this association. Seasonal effects on brain functions as measured by functional MRI (fMRI) have been observed both in resting-state (Choe et al. 2015) and when performing cognitive tasks (Meyer et al. 2016). Some neural transmitter activity in the striatum also showed seasonal effects, i.e. serotonin transmitter binding as measured by ^{11}C–labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([^{11}C]DASB) positron emission tomography (PET) (Praschak-Rieder et al. 2008; Kalbitzer et al. 2010; Mc Mahon et al. 2016) and dopamine synthesis as measured by ^{18}F-DOPA PET (Eisenberg et al. 2010; Kaasinen et al. 2012). A study even reported seasonal changes of hippocampal volumes in human subjects (Miller et al. 2015).

There are several limitations in these neuroimaging studies. First, most of these studies are cross-sectional, which is limited by the large individual differences in brain functions (Gordon et al. 2017). In addition, most of the studies examined roughly defined seasonal effects or yearly periodical effects. But the exact phase of the seasonal variations may be different from the roughly defined four seasons. Sometimes the yearly effects showed different phases (Meyer et al. 2016), suggesting more complicated relationships of environmental factors on brain functions. Therefore, it is critical to examine which environmental parameters such as weather have more contributions to the seasonal effects. Among different weather parameters, daylight length and temperature represent the significant environmental differences in seasonal fluctuations. Gillihan et al has explored the weather effects on brain functions using a small cross-sectional sample (Gillihan et al. 2011). They identified a weather index related to

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mood, and showed that the weather index was correlated with resting-state cerebral blood flow as measured by arterial spin labeled (ASL) perfusion fMRI mainly in the insula. But more systematic examinations of weather effects on brain functions have not been performed. Lastly, the most commonly used neuroimaging method is blood-oxygen-level dependent (BOLD) signal based fMRI, where the interpretation of the results should consider neuronal level, neurophysiological level, and the underlying physical level of the scanner. Specifically, if some effects on fMRI signals were observed, they may be due to the changes of neuronal activity, which is favorable to psychologists and psychiatrist. But the effects may also due to the changes of neurovascular coupling (Di et al. 2013; Yuan et al. 2013), changes of brain structures, or even the stability of the MRI scanner. Therefore, when examining the weather effects on brain functions, the alternative factors need to be considered and carefully controlled.

The purpose of the current study is to estimate to what extent resting-state brain functions were affected by weather. We analyzed longitudinal resting-state fMRI data from eight individuals from three datasets, where the individuals were scanned over periods of months to years (Choe et al. 2015; Poldrack et al. 2015; Filevich et al. 2017). One challenge for estimating weather effects is that the effects may be small. Therefore, we applied a machine learning regression approach to evaluate the amount of effects. Because multiple brain regions have been implicated in seasonal effects, e.g. basal ganglia (Praschak-Rieder et al. 2008; Kalbitzer et al. 2010; Mc Mahon et al. 2016), insula (Gillihan et al. 2011), and hippocampus (Miller et al. 2015), small regional effects may be aggregated into detectable effects using machine learning technique. We performed within-subject prediction analysis at single subject level. We asked what weather parameters have the most effects on resting-state brain functions, which can be represented as high prediction accuracies in predictions of these parameters. In order to rule out possible confounding effects that might give rise to prediction, we also performed control prediction analyses. First, we analyzed anatomical MRI images to check whether the observed prediction could be attributed to anatomical variations. Second, we checked images from phantom data to examine whether the prediction could be attributed to the stability of the MRI scanner.

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2. Materials and methods:

2.1. MRI datasets

Several multi-session resting-state fMRI datasets were pooled together, where the subjects were scanned over periods of months to years. The first subject was derived from the Kirby sample (Choe et al. 2015), where the single subject was scanned for 156 sessions over three and half years. The second subject was from the Myconnectome sample (Poldrack et al. 2015), where the subject was scanned 90 times over one and half years. The remaining six subjects were from the Day2day sample (Filevich et al. 2017), where the subjects were scanned over a similar span of about half a year. The detailed subject and scan information is listed in Table 1.

	Dataset	Sex	Age	# of sessions	First scan	Last scan	# of volumes	TR (s)	Voxel size (mm^3)
1	Kirby	M	40	156	2009/12/07	2013/06/20	198	2	3 x 3 x 4
2	MyConnectome	M	45	83	2012/10/23	2014/03/11	500	1.16	2.4 x 2.4 x 2.4
3	Day2day	F	23	50	2013/07/03	2013/12/18	148	2	3 x 3 x 3.6
4	Day2day	F	31	48	2013/07/03	2014/01/08	148	2	3 x 3 x 3.6
5	Day2day	F	29	45	2013/07/03	2014/01/27	148	2	3 x 3 x 3.6
6	Day2day	F	24	46	2013/07/02	2013/12/19	148	2	3 x 3 x 3.6
7	Day2day	M	30	39	2013/07/09	2014/02/12	148	2	3 x 3 x 3.6
8	Day2day	F	29	48	2013/07/03	2014/02/20	148	2	3 x 3 x 3.6

Table 1 Subject and scan information for the eight subjects with longitudinal scans. The number of sessions represents the effective number of sessions after dropout due to missing data or large head motions. The numbers of volumes represent the number of volumes used in the analysis after removing the first several volumes.

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The MRI data from the Kirby sample were scanned using a 3T Philips Achieva scanner. The data from the Myconnectome sample were scanned using a 3T Siemens Skyra scanner using a 32-channel head coil. And the data from the Day2day project were scanned using a 3T Siemens Magnetom Trio scanner using a 12-channel head coil. For each subject, resting-state fMRI data with multiple sessions were available. Within a subject, the resting-state fMRI were scanned using the same imaging parameters, but the parameters varied between different sites. Some essential resting-state fMRI parameters are listed in Table 1. For more details, we refer the readers to the original articles.

High resolution anatomical MRI images were available for only a few sessions in the Kirby and Myconnectome datasets for each subject. A MRI image of one session was used to register all the functional images to standard Montreal Neurological Institute (MNI) space. For the Day2day dataset, structural MRI images were available for all the sessions. Only the structural MRI image of the last session of each subject was used to aid preprocessing of the fMRI images. All the structural images of the Day2day project were also used in the control prediction analysis.

Lastly, we obtained MRI scanner quality assurance agar phantom data from the Day2day site. The images were scanned between June 2013 and February 2014 with a weekly basis (37 sessions in total). The data were acquired using gradient echo (GRE) sequence with the same coil as the one used for acquisition of the human data. Two images were acquired for each session. The parameters include: TR = 2000 ms; TE = 30 ms; FOV = 22 cm; matrix = 64 x 64; slice number = 28; slice thickness = 4 mm (1 mm gap).

2.2. Environmental data

The fMRI data were acquired from three different cities in two continents, Baltimore USA (Kirby), Austin USA (Myconnectome), and Berlin Germany (Day2day), which reflect different types of climates. The latitudes of these four cities are approximately 39 ^{o}N, 30 ^{o}N, and 52 ^{o}N, respectively. The weather data for the two US cities were downloaded from (US) National Centers for Environmental Information website (https://www.ncdc.noaa.gov/cdo-web/). The Local Climatological Data from Maryland Science

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Center Station and Austin Camp Mabry Station were used to represent the weather for the Kirby and Myconnectome datasets, respectively. We used the following measures, maximum and minimum temperatures, air pressure, wind speed, humidity, and precipitation. For those with missing data, we also checked Daily Summaries data from the NOAA website. The weather data for the Day2day dataset were collected by the German researchers. Daily sunshine hours were not used, because they were not available for the other datasets.

We also included daylight length in the current analysis. It was already available in the NOAA Local Climatological Data. For the Day2day data, we calculated the daylight length in Berlin according to its geographic location through the website of the Astronomical Applications Department of the U.S. Naval Observatory computes (http://aa.usno.navy.mil/data/docs/Dur_OneYear.php). For the Day2day dataset, there are also three parameters that reflect local environmental variations, i.e. scanner room temperature, scanner room humidity, and scanner Helium level. These three parameters were also used in the prediction analysis when using Day2day data to do prediction.

2.3. MRI data processing

2.3.1. Resting-state fMRI Preprocessing

Data processing and statistical analysis were performed using MATLAB (R2017b). SPM12 (http://www.fil.ion.ucl.ac.uk/spm/ ; RRID:SCR_007037) was used for fMRI data preprocessing. The first 2, 18, and 2 functional images for each session were discarded for Kirby, Myconnectome, and Day2day datasets, respectively, remaining 198, 500, and 148 images for each session. For each subject, all the functional images were realigned to the first session. All the prediction analysis was performed in native space of each subject. The anatomical images were coregistered to the mean functional image, and then segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and other tissues. At each voxel, Friston's 24 head motion model, the first five principle components from WM signals and the first five principle components from CSF signals were regressed out, and then a band-pass filtering was

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applied at frequency of 0.01 and 0.1 Hz. The images were not spatially smoothed, because there was no voxel-wise univariate analysis involved.

2.3.2. ALFF, ReHo, and connectivity matrices

We calculated three resting-state parameters to represent resting-state brain functions, i.e. amplitude of low-frequency fluctuation (ALFF) (Zang et al. 2007) and regional homogeneity (ReHo) (Zang et al. 2004) to represent regional properties, and connectivity matrix to represent inter-regional connectivity property. ALFF and ReHo were calculated using REST toolbox (Song et al. 2011). Essentially, ALFF calculated the power of the time series signals between 0.01 to 0.08 Hz at every voxel, resulting in an ALFF map for each session. ReHo calculated the correlations of the current voxel with the 26 neighboring voxels, which also resulted in a ReHo map for each session. The ALFF and ReHo values for each session within the subject's GM mask were concatenated as a vector for further analysis. The subject specific GM masks were defined as GM intensity greater than 0.5 based on the segmentation results from the subject's own anatomical image. Because the GM masks were defined in the native spaces and the fMRI resolution varies across datasets, the number of within mask voxels also varied (from 20,780 to 55,368).

Correlation matrices were calculated among 164 regions of interests (Dosenbach et al. 2010; Di and Biswal 2019). Spherical ROIs were first defined in MNI space with a radius of 8 mm, and transformed into the native space for each subject. There were in total 13,366 connectivity values (164 x (164 - 1) / 2), which were concatenated as a vector for the prediction analysis. The correlation values were transformed into Fishers' z scores.

2.3.3. Head motion and other potential confounding variables

To minimize the confounding of head motion in the prediction analysis, we first removed sessions with large head motions. We calculated frame-wise displacement in translation and rotation directions (Di and Biswal 2015). A session's data with maximum frame-wise displacement greater than 1 mm or 1^{o} were discarded. No sessions were removed in the Kirby data, and seven sessions (7.8%) were removed for the Myconnectome data. In the Day2day dataset, at most two sessions were removed for each subject.

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Secondly, we regressed out 24 motion variables using Friston's head motion model (Friston et al. 1996), which has been shown to be effective to minimize the effects of head motion on resting-state measures (Yan, Cheung, et al. 2013). Lastly, mean frame-wise displacement of both directions were regressed out from a predicted environmental variable before it was entered into the prediction analysis.

2.3.4. Structural MRI processing

For the Day2day dataset, the MPRAGE anatomical MRI images were available for all the sessions. Therefore, we used the anatomical images as a control condition for weather prediction. The analysis was also performed in subject's native space. The anatomical images from all the sessions of a subject were realigned and resliced to the image of the first session. Then each session's image was segmented separately, and the segmented tissue probability maps of GM, WM, and CSF were obtained in the native space. We defined GM, WM, and CSF masks as averaged probability greater than 0.5 in respective tissue type. GM, WM, and CSF probability in their masks were extracted, respectively, to be used in the prediction analysis.

2.3.5. Phantom image processing

For each session, the two images were realigned, and an averaged image was calculated. Because the phantom was placed in the similar location, no cross-session registration was performed. We first calculated correlations between daylight length and image values in every voxel, resulting in a correlation image. Next, a cubic mask in the center of the image was defined. The signals within the mask were extracted for the prediction analysis.

2.4. Prediction analysis

2.4.1. Prediction analysis scheme

The goal of the analysis is to estimate the prediction values of resting-state parameters on different weather or meteorological parameters. The analysis was performed for each of the resting-state parameters to predict each of the seven weather parameters. And we asked which weather parameters

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could be better predicted by which resting-state parameters. The prediction analysis was all done in a within-subject manner. Cross-validation was used to evaluate the prediction accuracy.

In addition to use these resting-state parameters, we also performed a series of control analysis to use other potential confounding parameters to predict the environmental parameters. First, we used the first fMRI image of each session after realignment to perform prediction analysis. Although the single image still reflects BOLD effects, it may be more contributed by brain structural variations. Secondly, to future rule out the structural contribution, we used segmented tissue probabilities of GM, WM, and CSF from their respective tissue masks to perform prediction analysis. Thirdly, we also extracted raw image values from the MPRAGE images in the three masks to serve as another control conditions. In addition, a cuboid mask was also defined for each subject, which was located outside the brain. The raw image values from the MPRAGE images from the air mask was used to control for baseline MRI signals. Finally, since all of the above mentioned analyses indicated prediction values to predict environmental parameters, especially daylight length, we further analyzed the quality assurance phantom data, and used the signals in the agar phantom area to perform prediction analysis to predict daylight length.

2.4.2. Machine learning regression analysis

We used linear machine learning regression model to perform prediction analysis. The general form of the prediction model is a linear regression model as the following:

$$y = X \cdot \beta + \varepsilon$$

where y is a $1 \times n$ vector of a predicted weather parameter, X is a $n \times m$ matrix of a resting-state parameter, β is the model parameters, and ε is the residual. N represents the number of observations, which in the current analysis were the number of sessions for the longitudinal data and the number of subjects for the cross-subject data. M represents the number of prediction variables, which could be the number of voxels in the ALFF or ReHo maps (see Table 1) or the number of connections (13,366) in the connectivity matrices. Here, m is much larger than n. Therefore, we used ridge regression to estimate the β

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parameters. Briefly speaking, instead of trying to achieve the goal of minimizing the sum of square means of the model prediction:

$$\min_{\beta} \sum (y - X \cdot \beta)^2$$

Ridge regression adds one more regularized term:

$$\min_{\beta} \sum (y - X \cdot \beta)^2 + \lambda \cdot \sum \|\beta\|^2$$

where λ represents the regularization parameter. The regularization term can constrain the sizes of beta values, thus preventing over fitting of the model. In the current analysis, we used the MATLAB function fitrlinear to perform the prediction analysis. There are other methods available, such as LASSO and elastic net, but a recent study suggested that ridge regression and elastic net can yield similar prediction accuracies while LASSO might perform worse in the scenario that the number of observations is much smaller than the number of features (Cui and Gong 2018).

There are three steps in the prediction analysis, 1) tuning regularization parameter λ to find the optimal λ (λ tuning), 2) training the model using the training dataset and the optimal λ to obtain a prediction model β (model training), and 3) estimating prediction accuracy by calculating correlations between predicted and actual values in a separate testing sample (cross-validation). Cross-validation was used to make sure that the estimated prediction accuracy was independent from the training data. Therefore, it is important for the within-subject and cross-subject prediction. For the between-subject prediction, however, prediction accuracy was estimated from a separate subject; therefore no cross-validation was required.

Because of the limited number of data in one fold (13 observations in the least case), 3-fold cross-validation was adopted. We used a nested tuning strategy to optimize the parameter λ (Figure 1A) (Cui and Gong 2018). Specifically, we first used 3-fold cross-validation to hold out one third of the data as an independent testing dataset, and used the remaining two thirds of the data as training and parameter tuning dataset. The data were first sorted according to the tested weather parameter, and the three folds

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were defined as the 1st, 4th, 7th, …, 2nd, 5th, 8th, …, and 3rd, 6th, 9th, … sessions of the data, respectively. Within the two thirds training and parameter tuning dataset, we first performed a nested loop of 3-fold analysis. Specifically, one third of the data were hold out, and the remaining of the two thirds of data were used to train the regression model using a set of λ values, from 10^{-5} to 10^{-1} in the logarithmic scale with a total 15 values. The one third of inner loop testing data was used to test the accuracy of the prediction by calculating the correlation between predicted and actual weather parameter values. This procedure was performed for three times for the three folds, and the mean accuracies were calculated for each of the λ values. The λ value with the highest mean accuracy was used for the outer layer training data to train the model. The model was then applied to the outer layer testing data to estimate prediction accuracies. The three accuracy values from the 3 folds were averaged to represent an estimate of accuracy for a subject.

3. Results

3.1. Weather predictions using the resting-state data

We first performed prediction analysis on different weather parameters using the ALFF maps, ReHo maps, connectivity matrices, as well as single frame of EPI images as a control condition (Figure 1). In general daylight length (DayL) and maximum and minimum environmental temperatures (T max and T min) had prediction accuracies. And daylight length usually had the highest prediction accuracies. All other environmental parameters had very low prediction accuracies. In terms of resting-state parameters, the ALFF map usually had the highest prediction value. The averaged prediction accuracy of daylight length was 0.42. However, using a single frame of EPI images could achieve comparable prediction accuracies as the ALFF maps.

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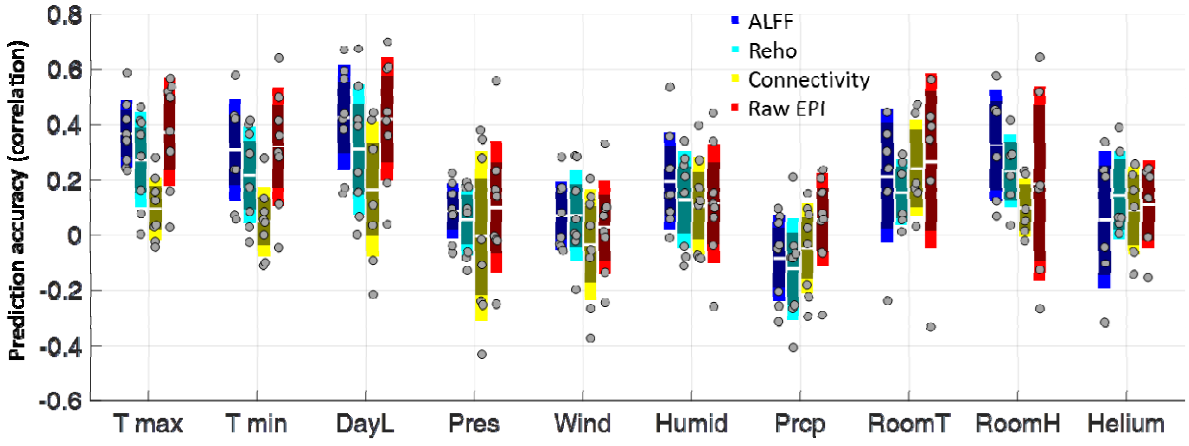

Figure 1 Prediction accuracies (correlations) of the ALFF (amplitude of low-frequency fluctuations) maps, ReHo (regional homogeneity) maps, and connectivity matrices on different weather parameters. Each dot represents one subject's mean prediction accuracy. The center white line and inner dark bar represent the mean and 95% confidence interval, respectively, and the outer light bar represents one standard deviation to the mean. One sample t test was performed for each condition, and the red * on the top represents statistical significant cross-subject effects at $p < 0.05$ after FDR (false discovery rate) correction for all the 21 predictions. The figure was made by using notBoxPlot (https://github.com/raacampbell/notBoxPlot).

It is still a question that whether the weather predictions using the resting-state parameters and single EPI are based on similar or different information. Since the daylight length had the highest prediction accuracies, we focused on its prediction. We combined ALFF with EPI or ReHo with EPI to predict daylight length to check whether combining the two modalities can boost the prediction accuracies. Unfortunately, combing two modalities yielded very similar prediction accuracies as those using single EPI images or ALFF images (Figure 2). Therefore, ALFF and ReHo did not convey more information than a single frame EPI image to predict daylight length.

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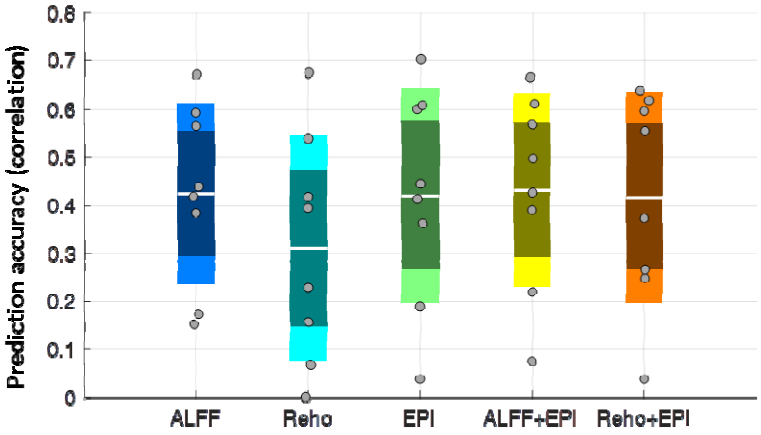

Figure 2 Prediction accuracies to daylight length using the ALFF, Reho, raw EPI maps, and the combination of EPI with ALFF or EPI.

3.2. Prediction analysis using the anatomical images

If single frame EPI images can predict weather parameter like daylight length, then the question becomes whether the prediction is due to brain functional activity, structural information, or other factors. We therefore performed the same prediction analysis using anatomical images, where were available in the six subject in the Day2day dataset. We first performed prediction analysis using segmented GM, WM, or CSF images using their respective tissue mask (Figure 3). The results showed very similar prediction patterns for different environmental parameters as using resting-state parameters. That is, the daylight length and environmental temperatures had the highest prediction accuracies. The prediction accuracies using all the three tissue probability maps were above 0.5, which were higher than using any resting-state parameters. However, what more interesting was that even higher prediction accuracies could be achieved using raw anatomical images in different tissue masks. The prediction accuracies were higher than 0.6 when using raw anatomical image signals in the GM or CSF masks. Finally, we defined a cuboid mask outside the brain (see Figure 4A as an example), and used the raw MRI signals in the mask to perform prediction analysis. Surprisingly, the analysis also showed similar pattern of prediction

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accuracies. The prediction accuracy on daylight length using the air mask was 0.47, which was lower than using all other anatomical parameters but still higher than using any of the resting-state parameters.

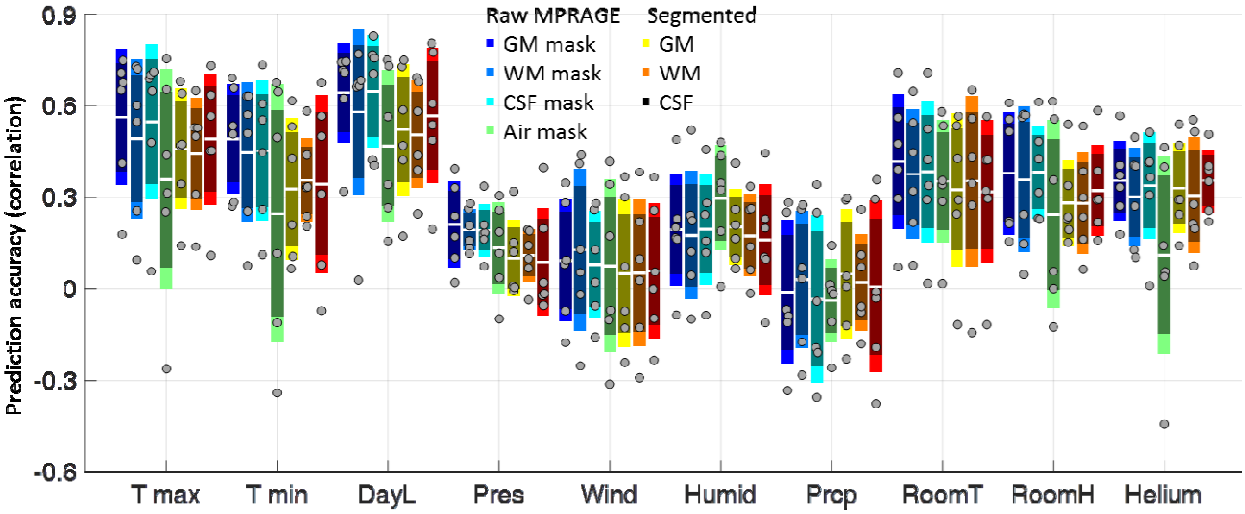

Figure 3 Cross-subject predictions of weather parameters using the amplitude of low-frequency fluctuations (ALFF) maps (top row), regional homogeneity (ReHo) maps (middle row), and connectivity matrices (bottom row) from the six subjects of the Day2day dataset. T max and T min represent daily maximum and minimum temperature, respectively.

To further explore the baseline MRI signals conveyed in the air mask, we calculated correlations between MPRAGE signals and daylight length in all the voxels in the air mask in all the six subjects (Figure 5B). There were small global effects of correlations between MPRAGE signals and daylight length. The global effects of correlations were strongly correlated with the prediction accuracies across subjects (Figure 5C), indicating that the global correlation is the driving information that gave rise to the prediction accuracy.

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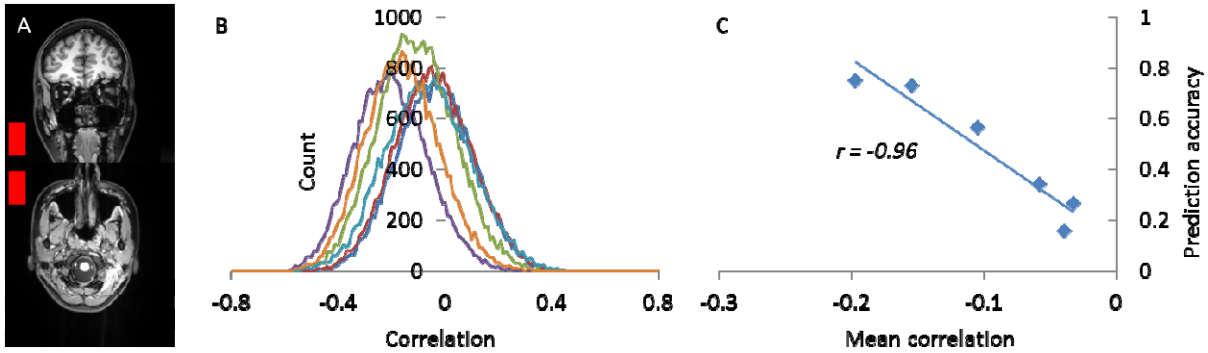

Figure 4 A) An example of the air mask from one subject overlaid to the subject's mean anatomical image. B) Histograms of the correlations between the MRI signals and daylight length of all the voxels in the air mask. Each line with different colors represents one subject. C) There is an extremely high negative correlation between the mean correlations in the air mask and the prediction accuracies of using the air mask voxels to predict daylight length.

3.3. Control analysis using the phantom images

To further confirm the baseline signal changes, we analyzed the weekly quality control phantom data around the same period of the Day2day project. We first calculated voxel-wise correlations between the MRI signal and daylight length (Figure 5A). It clearly showed that in the phantom region, there were high negative correlations. We defined a cubic mask in the center of the image, and the distribution of correlations of all the voxels in the mask were plotted in Figure 5B. The mean and median correlation in the cubic mask was *-0.75* and *-0.77*, respectively. Lastly, we performed the same kind of prediction analysis using all the voxels in the mask to predict daylight length, and the cross-validated mean accuracy was 0.72.

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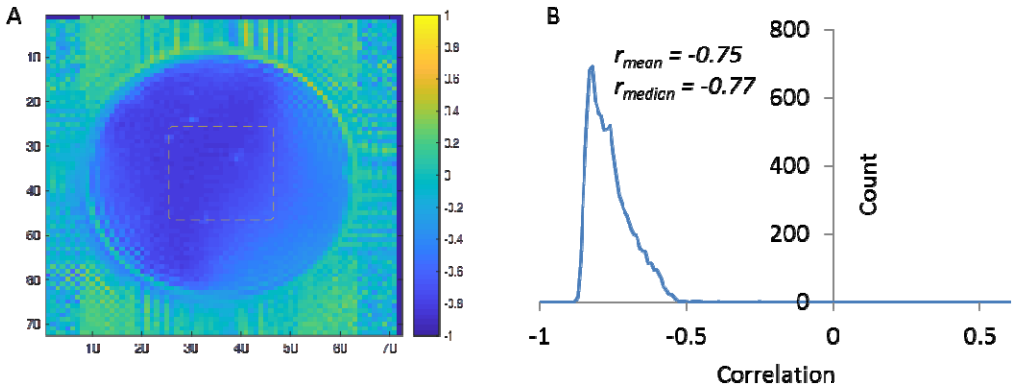

Figure 5 A) Voxel-wise Correlation maps between MRI image values and daylight length. The dash-line contour indicates the location of the cubic mask. B) Histogram of the correlations between MRI image values and daylight length in all the voxels in the cubic mask.

4. Discussion

By applying machine learning regression to longitudinal fMRI data that were scanned over months to years, we demonstrated that we can predict environmental parameters, especially daylight length and temperature, by using resting-state fMRI parameters. However, a series of control analysis showed that using a single EPI image, segmented tissue images, and raw MPRAGE image signals in different tissue masks and even in a mask outside the brain could all predict the environmental parameters. The resting-state parameters did not add prediction values to single frame EPI images. These results indicated the prediction of weather parameters, especially daylight length, cannot be explained as the weather effects on brain functions. Rather, the prediction may reflect MRI scanner baseline signal variations that were affected by environmental parameters. The analysis of the quality control phantom images supported our speculation.

Among all the environmental parameters analyzed the daylight length had the highest prediction accuracies. It's noteworthy that the prediction accuracies of daylight length were even higher than what in the predictions of MRI scanner room temperature and humidity. Therefore, there may be some other

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local factors that mediate the effects of daylight length on scanner stability. A study has shown that the gaseous oxygen level in the magnet field can influence the MRI signals (Bates et al. 1995). It is reasonable to speculate that the oxygen level in the scanner room may fluctuate across seasons due to different ventilation conditions. In addition, the cooling systems of the scanner may be affected by either electricity supply stability or cooling water temperature. Given that the MRI is such a sophisticated machine, there may be other factors that mediate the association between daylight length and scanner stability.

The current results highlighted the difficulty to study long term effects such as weather on brain structures and functions using MRI. Consistent with two previous fMRI studies (Choe et al. 2015; Meyer et al. 2016), we did find weather effects on fMRI measures. But we demonstrated that the weather effects are likely due to the variations of MRI scanner stability. It is reasonable to speculate that MRI scanner stability might contribute to the reported seasonal effects (Choe et al. 2015; Meyer et al. 2016). We also showed that tissue probability measures of GM volumes may also be affected by the scanner stability, so brain volumetric measures may also be affected by the scanner stability (Miller et al. 2015). The problem may arise from the fact that most of the fMRI/MRI measures are relative measures. If absolute measures can be used, e.g. using perfusion measures from arterial spin labeling (ASL) (Detre et al. 1992, 2012), then the effects from scanner stability may be minimized. In addition, adjusting global signals maybe helpful to minimize the scanner stability issue (Peelle et al. 2012; Yan, Craddock, et al. 2013). But at the same time, the global signal was tightly coupled with neural activity (Scholvinck et al. 2010), and adjusting global signals may cause statistical artifacts (Murphy et al. 2009; Saad et al. 2012).

The current analysis demonstrated that machine learning is a powerful method to be able to pick up small effects. The phantom data showed the correlations between baseline MRI signals and daylight length were about 0.7. Although the direct correlations of MRI signals and daylight length when scanning human participants were blurred (Figure 4A), we could still achieve the similar level as the prediction accuracies by using machine learning and cross-validation (Figure 3). Indeed, the cross-

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validated prediction accuracies were between 0.6 and 0.7, which were very close to the correlation in the phantom data. Machine learning methods have become more and more popular in studying brain-behavior relationships (Finn et al. 2015; Cui and Gong 2018) and different mental disorders (Whelan et al. 2014). It is powerful on one hand, but on the other hand, careful control conditions are needed to rule out possible confounding artifacts.

In conclusion, by applying machining learning on resting-state fMRI or structural MRI data, we can predict several weather parameters, with the highest prediction accuracies to daylight length. However, the predictions were not likely due to the weather effects on brain functions or structures, but may due to the weather effects on the stability of MRI scanners. The data highlight the difficulty to use fMRI/MRI data to study long term effects. And call for cautions to control for scanner stability when studying long term effects.

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References:

Bates S, Yetkin Z, Jesmanowicz A, Hyde JS, Bandettini PA, Estkowski L, Haughton VM. 1995. Artifacts in functional magnetic resonance imaging from gaseous oxygen. J Magn Reson Imaging. 5:443–445.

Cedeño Laurent JG, Williams A, Oulhote Y, Zanobetti A, Allen JG, Spengler JD. 2018. Reduced cognitive function during a heat wave among residents of non-air-conditioned buildings: An observational study of young adults in the summer of 2016. PLOS Med. 15:e1002605.

Choe AS, Jones CK, Joel SE, Muschelli J, Belegu V, Caffo BS, Lindquist MA, Van Zijl PCM, Pekar JJ. 2015. Reproducibility and temporal structure in weekly resting-state fMRI over a period of 3.5 years.

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PLoS One. 10.

Cui Z, Gong G. 2018. The effect of machine learning regression algorithms and sample size on individualized behavioral prediction with functional connectivity features. Neuroimage.

Denissen JJA, Butalid L, Penke L, van Aken MAG. 2008. The effects of weather on daily mood: A multilevel approach. Emotion. 8:662–667.

Detre JA, Leigh JS, Williams DS, Koretsky AP. 1992. Perfusion imaging. Magn Reson Med. 23:37–45.

Detre JA, Rao H, Wang DJJ, Chen YF, Wang Z. 2012. Applications of arterial spin labeled MRI in the brain. J Magn Reson Imaging. 35:1026–1037.

Di X, Biswal BB. 2015. Characterizations of resting-state modulatory interactions in the human brain. J Neurophysiol. 114:2785–2796.

Di X, Biswal BB. 2019. Toward Task Connectomics: Examining Whole-Brain Task Modulated Connectivity in Different Task Domains. Cereb Cortex. 29:1572–1583.

Di X, Kannurpatti SS, Rypma B, Biswal BB. 2013. Calibrating BOLD fMRI Activations with Neurovascular and Anatomical Constraints. Cereb Cortex. 23:255–263.

Dosenbach NUF, Nardos B, Cohen AL, Fair DA, Power JD, Church JA, Nelson SM, Wig GS, Vogel AC, Lessov-Schlaggar CN, Barnes KA, Dubis JW, Feczko E, Coalson RS, Pruett JR, Barch DM, Petersen SE, Schlaggar BL. 2010. Prediction of individual brain maturity using fMRI. Science. 329:1358–1361.

Eisenberg DP, Kohn PD, Baller EB, Bronstein JA, Masdeu JC, Berman KF. 2010. Seasonal Effects on Human Striatal Presynaptic Dopamine Synthesis. J Neurosci. 30:14691–14694.

Filevich E, Lisofsky N, Becker M, Butler O, Lochstet M, Martensson J, Wenger E, Lindenberger U, Kühn S. 2017. Day2day: investigating daily variability of magnetic resonance imaging measures over half a year. BMC Neurosci. 18:65.

Finn ES, Shen X, Scheinost D, Rosenberg MD, Huang J, Chun MM, Papademetris X, Constable RT. 2015. Functional connectome fingerprinting: identifying individuals using patterns of brain

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connectivity. Nat Neurosci. 18:1664–1671.

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. 1996. Movement-related effects in fMRI time-series. Magn Reson Med. 35:346–355.

Gillihan SJ, Detre JA, Farah MJ, Rao H. 2011. Neural Substrates Associated with Weather-Induced Mood Variability: An Exploratory Study Using ASL Perfusion fMRI. J Cogn Sci (Seoul). 12:195–210.

Gordon EM, Laumann TO, Gilmore AW, Newbold DJ, Greene DJ, Berg JJ, Ortega M, Hoyt-Drazen C, Gratton C, Sun H, Hampton JM, Coalson RS, Nguyen AL, McDermott KB, Shimony JS, Snyder AZ, Schlaggar BL, Petersen SE, Nelson SM, Dosenbach NUF. 2017. Precision Functional Mapping of Individual Human Brains. Neuron. 95:791–807.e7.

Hirshleifer D, Shumway T. 2003. Good Day Sunshine: Stock Returns and the Weather. J Finance. 58:1009–1032.

IJzerman H, Lindenberg S, Dalğar İ, Weissgerber SSC, Vergara RC, Cairo AH, Čolić M V., Dursun P, Frankowska N, Hadi R, Hall CJ, Hong Y, Hu C-P, Joy-Gaba J, Lazarević D, Lazarević LB, Parzuchowski M, Ratner KG, Rothman D, Sim S, Simão C, Song M, Stojilović D, Blomster JK, Brito R, Hennecke M, Jaume-Guazzini F, Schubert TW, Schütz A, Seibt B, Zickfeld JH, Vazire S, McCarthy R. 2018. The Human Penguin Project: Climate, Social Integration, and Core Body Temperature. Collabra Psychol. 4.

Kaasinen V, Jokinen P, Joutsa J, Eskola O, Rinne JO. 2012. Seasonality of striatal dopamine synthesis capacity in Parkinson's disease. Neurosci Lett. 530:80–84.

Kalbitzer J, Erritzoe D, Holst KK, Nielsen FÅ, Marner L, Lehel S, Arentzen T, Jernigan TL, Knudsen GM. 2010. Seasonal Changes in Brain Serotonin Transporter Binding in Short Serotonin Transporter Linked Polymorphic Region-Allele Carriers but Not in Long-Allele Homozygotes. Biol Psychiatry. 67:1033–1039.

Keller MCM, Fredrickson BL, Ybarra O, Cote S, Johnson K, Mikels J, Conway A, Wager T, Côté S, Johnson K, Mikels J, Conway A, Wager T. 2005. A warm heart and a clear head. The contingent

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464 effects of weather on mood and cognition. Psychol Sci. 16:724–731.

465 Kurlansik SL, Ibay AD. 2012. Seasonal affective disorder. Am Fam Physician. 86:1037–1041.

466 Lim ASP, Gaiteri C, Yu L, Sohail S, Swardfager W, Tasaki S, Schneider JA, Paquet C, Stuss DT,
467 Masellis M, Black SE, Hugon J, Buchman AS, Barnes LL, Bennett DA, De Jager PL. 2018.
468 Seasonal plasticity of cognition and related biological measures in adults with and without
469 Alzheimer disease: Analysis of multiple cohorts. PLOS Med. 15:e1002647.

470 Mc Mahon B, Andersen SB, Madsen MK, Hjordt L V., Hageman I, Dam H, Svarer C, da Cunha-Bang S,
471 Baaré W, Madsen J, Hasholt L, Holst K, Frokjaer VG, Knudsen GM. 2016. Seasonal difference in
472 brain serotonin transporter binding predicts symptom severity in patients with seasonal affective
473 disorder. Brain. 139:1605–1614.

474 Meyer C, Muto V, Jaspar M, Kussé C, Lambot E, Chellappa SL, Degueldre C, Balteau E, Luxen A,
475 Middleton B, Archer SN, Collette F, Dijk D-J, Phillips C, Maquet P, Vandewalle G. 2016.
476 Seasonality in human cognitive brain responses. Proc Natl Acad Sci. 113:3066–3071.

477 Miller MA, Leckie RL, Donofry SD, Gianaros PJ, Erickson KI, Manuck SB, Roecklein KA. 2015.
478 Photoperiod is associated with hippocampal volume in a large community sample. Hippocampus.
479 25:534–543.

480 Murphy K, Birn RM, Handwerker DA, Jones TB, Bandettini PA. 2009. The impact of global signal
481 regression on resting state correlations: are anti-correlated networks introduced? Neuroimage.
482 44:893–905.

483 Peelle JE, Cusack R, Henson RNA. 2012. Adjusting for global effects in voxel-based morphometry: gray
484 matter decline in normal aging. Neuroimage. 60:1503–1516.

485 Poldrack RA, Laumann TO, Koyejo O, Gregory B, Hover A, Chen M-Y, Gorgolewski KJ, Luci J, Joo SJ,
486 Boyd RL, Hunicke-Smith S, Simpson ZB, Caven T, Sochat V, Shine JM, Gordon E, Snyder AZ,
487 Adeyemo B, Petersen SE, Glahn DC, Reese Mckay D, Curran JE, Göring HHH, Carless MA,
488 Blangero J, Dougherty R, Leemans A, Handwerker DA, Frick L, Marcotte EM, Mumford JA. 2015.

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Long-term neural and physiological phenotyping of a single human. Nat Commun. 6:8885.

Praschak-Rieder N, Willeit M, Wilson AA, Houle S, Meyer JH. 2008. Seasonal Variation in Human Brain Serotonin Transporter Binding. Arch Gen Psychiatry. 65:1072.

Saad ZS, Gotts SJ, Murphy K, Chen G, Jo HJ, Martin A, Cox RW. 2012. Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. Brain Connect. 2:25–32.

Saunders EM. 1993. Stock prices and Wall Street weather. Am Econ Rev. 83:1337–1345.

Scholvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. 2010. Neural basis of global resting-state fMRI activity. Proc Natl Acad Sci. 107:10238–10243.

Song X-W, Dong Z-Y, Long X-Y, Li S-F, Zuo X-N, Zhu C-Z, He Y, Yan C-G, Zang Y-F. 2011. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One. 6:e25031.

Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, Barker GJ, Bokde ALW, Büchel C, Carvalho FM, Conrod PJ, Flor H, Fauth-Bühler M, Frouin V, Gallinat J, Gan G, Gowland P, Heinz A, Ittermann B, Lawrence C, Mann K, Martinot J-L, Nees F, Ortiz N, Paillère-Martinot M-L, Paus T, Pausova Z, Rietschel M, Robbins TW, Smolka MN, Ströhle A, Schumann G, Garavan H, Albrecht L, Arroyo M, Aydin S, Bach C, Barbot A, Bricaud Z, Bromberg U, Bruehl R, Cattrell A, Czech K, Dalley J, Desrivieres S, Fadai T, Fuchs B, Gollier Briand F, Head K, Heinrichs B, Heym N, Hübner T, Ihlenfeld A, Ireland J, Ivanov N, Jia T, Jones J, Kepa A, Lanzerath D, Lathrop M, Lemaitre H, Lüdemann K, Martinez-Medina L, Mignon X, Miranda R, Müller K, Nymberg C, Pentilla J, Poline J-B, Poustka L, Rapp M, Ripke S, Rodehacke S, Rogers J, Romanowski A, Ruggeri B, Schmäl C, Schmidt D, Schneider S, Schroeder M, Schubert F, Sommer W, Spanagel R, Stacey D, Steiner S, Stephens D, Strache N, Struve M, Tahmasebi A, Topper L, Vulser H, Walaszek B, Werts H, Williams S, Peng Wong C, Yacubian J, Ziesch. V. 2014. Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature. advance on.

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514 Yan C-G, Craddock RC, Zuo X-N, Zang Y-F, Milham MP. 2013. Standardizing the intrinsic brain:
515 Towards robust measurement of inter-individual variation in 1000 functional connectomes.
516 Neuroimage. 80:246–262.
517 Yan CG, Cheung B, Kelly C, Colcombe S, Craddock RC, Di Martino A, Li Q, Zuo XN, Castellanos FX,
518 Milham MP. 2013. A comprehensive assessment of regional variation in the impact of head
519 micromovements on functional connectomics. Neuroimage. 76:183–201.
520 Yuan R, Di X, Kim EH, Barik S, Rypma B, Biswal BB. 2013. Regional homogeneity of resting-state
521 fMRI contributes to both neurovascular and task activation variations. Magn Reson Imaging.
522 31:1492–1500.
523 Zang Y-F, He Y, Zhu C-Z, Cao Q-J, Sui M-Q, Liang M, Tian L-X, Jiang T-Z, Wang Y-F. 2007. Altered
524 baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev.
525 29:83–91.
526 Zang Y, Jiang T, Lu Y, He Y, Tian L. 2004. Regional homogeneity approach to fMRI data analysis.
527 Neuroimage. 22:394–400.
528