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Prediction of individual season of birth using MRI

Spiro P. Pantazatos¹

Spiro P. Pantazatos: spiropant@gmail.com

¹Department of Psychiatry, Columbia University Medical Center, New York, NY, USA

Abstract

Previous research suggests statistical associations between season of birth (SOB) with prevalence of neurobehavioral disorders such as schizophrenia and bipolar disorder, personality traits, and suicidal behavior. These effects are thought to be mediated by seasonal differences in perinatal photoperiod, which was recently shown to imprint circadian clock neurons and behavior in rodents. However, it is unknown whether SOB is associated with any measurable differences in the normal human adult brain, and whether individual SOB can be deduced based on phenotype. Here I show that SOB predicts neuroanatomical differences in regional grey matter volume, and that MRI scans carry spatially distributed information allowing significantly above chance prediction of an individual's SOB. Using an open source database of over 550 structural brain scans, Voxel-Based Morphometry (VBM) analysis showed a significant SOB effect in left superior temporal gyrus (STG) in males ($p=0.009$, FWE whole-brain corrected), with greater grey matter volumes in fall and winter births. A cosinor analysis revealed a significant annual periodicity in left STG grey matter volume (Zero Amplitude Test: $p<5\times 10^{-7}$), with a peak towards the end of December and a nadir towards the end of June, suggesting that perinatal photoperiod accounts for this SOB effect. Whole-brain VBM maps were used as input features to multivariate machine-learning based analyses to classify SOB. Significantly greater than chance prediction was achieved in females (overall accuracy 35%, $p<0.001$), but not in males (overall accuracy 26%, $p=0.45$). Pair-wise binary classification in females revealed the highest discrimination was obtained for winter vs. summer classification (peak area under the ROC curve=0.71, $p<0.0005$). Discriminating regions included fusiform and middle temporal gyrus, inferior and superior parietal lobe, cerebellum, and dorsolateral and dorsomedial prefrontal cortex. Results indicate SOB is detectable with MRI, imply SOB exerts effects on the developing human brain that persist through adulthood, and suggest neuroimaging may be a valuable intermediate phenotype in bridging the gap between SOB and personality and neurobehavioral disorders.

Keywords

birth season; seasonal biology; neural development; IXI database; brain structure; pattern recognition

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Introduction

Previous research suggests statistical associations between season of birth (SOB) with prevalence of neurobehavioral disorders such as schizophrenia (Davies et al., 2003; Hori et al., 2012a; Bersani et al., 2006; Cohen and Najolia, 2011; Torrey et al., 1997), bipolar disorder (Torrey et al., 1997) and panic disorder (Castrogiovanni et al., 1999), and traits such as lifespan (Doblhammer and Vaupel, 2001), novelty and sensation seeking (Eisenberg et al., 2007; Roussos et al., 2010; Chotai et al., 2009a) and suicidality (Woo et al., 2012; Salib and Cortina-Borja, 2006). Proposed explanations for these associations include variations in infectious disease exposure, nutrition, temperature, maternal hormones, maternal egg quality, birth complications and photoperiod (Jongbloet et al., 2005; Doblhammer and Vaupel, 2001; Schwartz, 2011). Perinatal photoperiod may impact the dopamine-melatonin balance regulating circadian and seasonal rhythms and serotonin turnover (Natale et al., 2009; Chotai and Adolfsson, 2002; Chotai and Asberg, 1999), and was recently shown to imprint circadian clock neurons and behavior in rodents (Ciarleglio et al., 2011). Additional lines of evidence suggest maternal inflammation and infection (which are more likely during flu season) account for SOB associations in schizophrenia (Brown, 2011). Prenatal vitamin D, which is influenced by prenatal photoperiod (Grytten et al., 2013), has also been shown to be a risk modifying factor for many chronic diseases such as rickets, multiple sclerosis, schizophrenia, heart disease, autism and cancer (Kaludjerovic and Vieth, 2010).

Given prior reports, it was hypothesized that the penetrance of SOB effects may be greater at the level of relatively more simple, biologically based phenotypes such as brain structure. Here, Voxel-Based Morphometry (VBM) was applied to an open-source database that included over 550 adult structural brain scans and birth-date information. Two primary hypotheses were tested: 1) SOB is associated with measurable differences in local grey matter volume, particularly in regions associated with schizophrenia and/or novelty and sensation seeking traits, and 2) multivariate pattern recognition approaches that can detect subtle and spatially complex patterns of local volume differences (Lao et al., 2004) would allow above-chance prediction of individual SOB. Multivariate pattern analysis was applied to the VBM data since the effectiveness of voxel-based (univariate) statistics is significantly biased toward group differences that are highly localized in space and of linear nature, whereas it is significantly reduced in cases with group differences of similar or even higher magnitude, when these differences are spatially complex and subtle (Davatzikos, 2004). Thus both univariate and multivariate approaches were used in order to detect both highly localized structural differences as well as subtle and distributed effects. Positive findings with either approach would imply that SOB results in persistent and lasting effects on brain structure and would suggest the use of neuroimaging as an intermediate phenotype in bridging the gap between SOB and personality and behavioral disorders.

Materials and Methods

Participants and image acquisition

T1-weighted MRI scans of over 550 normal, healthy adults and associated demographic data (including birthdates) were obtained from the publicly-accessible IXI database (<http://biomedic.doc.ic.ac.uk/brain-development/index.php?n=Main.Datasets>). Data was acquired

from three hospital scanners affiliated with Imperial College in London, England (Philips 1.5T, General Electric 1.5T, Philips 3T). See above link for scan parameters. This dataset was used in a recent study which estimated age from T1-weighted MRI scans (Franke et al., 2010). As London includes a diverse immigrant population there was likely a small to medium percentage of equatorial and Southern Hemisphere (i.e. Australia) births among the dataset. Unfortunately, the demographic information of this dataset do not include birthplace data, so it was impossible to stratify or exclude subjects according to hemisphere and latitude. Since seasons in the Southern Hemisphere are opposite to those in the Northern Hemisphere, this limitation may potentially impact Type 2 error rates (i.e. probability of a false negative, see limitations section for further discussion). Subject demographic data across the four seasons are presented in Supplementary Table 1.

Image analyses

VBM preprocessing—Anatomical data were processed with whole-brain VBM (Ashburner and Friston, 2000), implemented in SPM8 (v4667) software (<http://www.fil.ion.ucl.ac.uk/spm>) with Matlab (version 7.13, Mathworks, Natick, Massachusetts) on 64-bit Ubuntu 12.04.1 LTS OS. Three-dimensional T1-weighted images were segmented into the three main tissue classes (GM, white matter [WM], and cerebrospinal fluid) with the SPM unified segmentation algorithm (Ashburner and Friston, 2005). The GM and WM images were next spatially normalized to a group specific template and then to Montreal Neurological Institute space with a diffeomorphic image registration toolkit (Diffeomorphic Anatomical Registration using Exponentiated Lie algebra) in 1.5-mm cubic resolution (Ashburner, 2007). The images were modulated with the individual Jacobian determinants to preserve the local amount of GM and WM. Modulation was achieved by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. In effect, the analysis of modulated data tests for regional differences in the absolute amount of GM. Finally, images were smoothed with an 8-mm full-width-at-half-maximum isotropic Gaussian kernel. This is the SPM default, optimal for group inference (Mikl et al., 2008), and commonly used in VBM studies.

VBM univariate analysis—Before statistical analysis, an inclusion mask was created by absolute thresholding, which excluded all voxels with GM values < 0.2 . Statistical analysis on processed GM images was carried out by means of whole brain 1-way ANCOVA (SOB as 1st factor) in males and females separately. Consistent with many previous SOB studies (Reid and Zborowski, 2006; Cohen and Najolia, 2011; Natale et al., 2009; Hori et al., 2012b; Tonetti et al., 2012) seasons were defined according to the Astronomical definition (i.e., seasons dividing according to the spring equinox on March 20th or 21st, summer solstice on June 20th or 21st, the fall equinox on September 22nd or 23rd, and the winter solstice on December 21st or 22nd). The exact day of solstice and equinox vary from year to year, therefore birthdates within one day of these dates were excluded resulting in the following seasonal definitions used in the current analysis (Winter: December 23rd thru March 19th, Spring: March 22nd – June 19th, Summer: June 22nd – September 21st, Fall: September 24th thru December 20th). These excluded birthdates accounted for 8/6 female/male participants which were omitted from subsequent analyses. Age, its interaction with SOB, total intracranial volume (TIV, which was the sum of GM, WM, and cerebrospinal

fluid, for each subject normalized by 10,000) and scanner source (2 vectors of ones corresponding to 2 of the 3 scanners) were entered as covariates. Age, TIV and scanner source were included because these are independently associated with GM differences in adults, and failure to adjust for these variables can result in false positives (Shokouhi et al., 2011; Henley et al., 2010)(see Supplemental Figure 1 for design matrix and Supplemental Figure 2 for effects of scanner in these data). For whole-brain analyses, maps were thresholded at $p < 0.05$ FWE corrected. Additionally, significant clusters were searched by means of non-stationary cluster extent correction with random fields (Hayasaka et al., 2004) as implemented with the NS toolbox (<http://fmri.wfubmc.edu/cms/software#NS>) for SPM5. This correction method confers increased sensitivity to spatially extended signals while remaining valid when cluster-size distribution varies, depending on local smoothness as is the case in VBM data. The Marsbar Toolbox (<http://marsbar.sourceforge.net/>) was used to conduct ROI analyses. For effect size calculations t-values obtained from the above ANCOVA were converted to Cohen's d using the formula $d = 2 * t / \sqrt{df}$.

Cosinor analysis (Nelson et al., 1979) was used to test for cyclical effects in monthly mean GM volumes extracted from the left STG ROI (defined from the above whole-brain analysis thresholded at $p < 0.05$ FWE). Briefly, this method uses least squares to fit a cosine waveform with a given period (here defined as 12 months) to the data. It estimates three parameters: overall mean, amplitude and acrophase (i.e. time point of peak amplitude relative to the 1 time point, here January). The amplitude parameter estimate and its associated p-value (statistical difference from zero) was used to infer the presence of significant cyclical effects with an annual periodicity (12 months). For this analysis the Cosinor Analysis Matlab Toolbox was used (<http://www.mathworks.com/matlabcentral/fileexchange/20329-cosinor-analysis/content/html/cosinor.html>).

Pattern recognition of VBM to predict SOB—Prior to pattern analysis, voxels were resampled from $1.5 \times 1.5 \times 1.5$ mm resolution to $6 \times 6 \times 6$ mm to reduce computational load, and features were corrected for effects of age (but not its interaction with SOB), scanner, and TIV. Because female participants from the IOP scanner were unevenly distributed across the seasons (see Supplementary Table 1), female pattern recognition experiments only included data from Guys and HH scanner. To include more voxels/features in the classification task, the implicit mask threshold was dropped from 0.2 to 0.05. Thus, features/voxels were extracted from an SPM model similar to the 1-way ANCOVA VBM univariate analysis, but with the exception that it referenced $6 \times 6 \times 6$ mm input data which was implicitly masked at a threshold=0.05, and included nuisance covariates for scanner, age (no SOBxage interaction) and TIV. Two types of classifications were performed: a multiclass classification with four classes (winter, spring, summer, fall) and six pair-wise binary classifications between each unique season pair.

For multiclass classification, a one vs. one linear kernel SVM with initial filter feature selection, leave-one-out cross validation, and Recursive Feature Elimination (RFE) was implemented using the Spider v1.71 Matlab toolbox (<http://people.kyb.tuebingen.mpg.de/spider/>) with default regularization parameter $C=1$. During each iteration of leave-one-out cross validation, one subject was withheld from the dataset and 1) a 1-way ANOVA (SOB as factor) was performed over the remaining training data and the top 10% of features (voxels)

were selected based on F-score 2) feature dimensionality reduction (PCA) was then applied to these remaining features 3) using one_vs_one SVM, a grid selection procedure with 5-fold nested cross-validation was used to select the optimal number of features (PCs) from a range of [10, 20, 30...240] using RFE (see below for more details) 4) features that were selected in the initial filter (step 1 above) were extracted from the test example, and were projected onto reduced feature space determined in step 2 above 5) using the optimal number of features (determined in step 3), a model was fit using the entire training sample and was then applied to predict the class of the left out test sample. In step 3 above, RFE was implemented as in (Guyon et al., 2002) to select the top [10:10:240] features, and the optimal number of features was determined using 5-fold nested cross-validation (i.e. within each training set, RFE was applied 24×5 times). This grid selection procedure was implemented using the following object-oriented Spider code in Matlab:

```
>> a1=param(rfe(one_vs_one(svm(kernel('linear')))), 'feat', [10:10:240]);
>> a2=gridsel(a1);
```

The first line above is used to create a set of SVM one vs. one linear kernel algorithms (a1) with different number of top N features (selected through RFE). The second line finds the best of the algorithm from the set a1 using 5-fold cross validation, and trains and stores that model in a2.

Binary SVM learning and classification was done using the Spider v1.71 Matlab toolbox (<http://people.kyb.tuebingen.mpg.de/spider/>) using default regularization parameter $C=1$. For each pair-wise binary classification, a linear kernel SVM (Vapnik, 1999) with initial filter feature selection (t-test), feature dimensionality reduction (PCA), and leave-one-out cross validation was used. During each iteration of leave-one-out cross validation, one subject was withheld from the dataset and 1) a 2-sample t-test was performed over the remaining training data and the top 10% of features (voxels) were selected based on absolute t-score 3) feature dimensionality reduction (PCA) was then applied to these remaining features, and principal components (PCs) that explained 50%, 60%, 70%, 80%, 90% and 95% of the total variance were used to train six SVM models respectively 4) features that were selected in the initial filter (step 1 above) were extracted from the test example, and were back-projected onto reduced feature space determined in step 3 above 5) finally the trained models from step 3 were applied to these reduced-space features to predict the class of the test example.

Classification performance for multiclass classification is reported in terms of sensitivity and specificity for each of the four seasons and overall accuracy. Due to the relatively high computational demands of leave-one-out cross validation with model selection and nested cross-validation of a multiclass SVM with ~250 examples, it was not practical to use a non-parametric permutation approach to estimate significance of overall accuracy. Instead, Cohen's Kappa coefficient (κ), a widely used and well-validated statistical measure for estimating inter-rater reliability, was used to quantify performance significance. In this case, "rater 1" is the true SOB label for each participant, and "rater 2" is the SOB predicted by the multiclass machine. Since κ takes into account agreement occurring by chance, it is a more robust measure than simple percent agreement (overall accuracy). Cohen's Kappa was computed from the resulting 4×4 confusion matrix using the formula:

$$\kappa = \frac{Pr(a) - Pr(e)}{1 - Pr(e)},$$

where $Pr(a)$ is the overall accuracy, and $Pr(e)$ is the hypothetical probability of chance agreement using the observed data. For a description of how $Pr(e)$ is calculated see (Cohen, 1960). The variance of κ was also computed using Congalton's delta method (Congalton and Green, 2008) and was used to estimate 90% CI and a Z-score and associated one-sided p-value. Calculations were performed using the `assessment.m` function which is part of the MATLAB Active Learning Toolbox for Remote Sensing (code.google.com/p/altoolbox).

Classification performance for six pair-wise binary SVMs is reported in terms of “area under the curve” (AUC) (i.e. area under the receiver operator characteristic, or ROC curve (Hanley and McNeil, 1982)). Since the predicted labels are binary (not continuous scores), AUC is identical to the arithmetic mean of sensitivity (true positive rate) and specificity (true negative rate). For each pair-wise comparison, the maximum AUC across the six SVM models (corresponding to the increasing number of reduced-space features) was determined. This AUC was compared to maximum AUCs obtained from non-parametric permutation tests (Natale et al., 2002) (2000 iterations) to confer significance relative to a null distribution. Confidence intervals (CI) for AUC estimates from real data were estimated using the ‘bootstrap t’ approach (Arenaza-Urquijo et al., 2013) with 10,000 iterations using the Measures of Effect Size Toolbox (<http://www.mathworks.com/matlabcentral/fileexchange/32398-measures-of-effect-size-toolbox>), while CIs for the null hypothesis estimate were computed directly from the null distribution.

Results

Effects of SOB on local grey matter volume

A separate SPM ANCOVA model in males and females was estimated to identify regions whose grey matter volume was predicted by SOB. In males, a significant effect was observed in the left superior temporal gyrus (STG) (Figure 1A, $p < 0.05$ FWE, cluster size=19; peak at MNI [-58 -9 0], $F=11.64$, $p=0.009$ FWE corrected). A plot of beta estimates revealed this effect was driven by greater GM volumes in fall and winter births relative to spring and summer (Figure 1B). In females, no voxels survived correction for multiple comparisons across the whole-brain. There were no significant ageXSOb interaction effects in either males or females ($p < 0.05$ FWE).

A post-hoc t-test for fall and winter > spring and summer in the STG peak voxel yielded $t_{(234)}=5.22$, which is equivalent to a Cohen's $d = 0.68$. This was compared to the peak effect size observed with age, as GM volume is known to be significantly reduced with age in frontal cortical structures. Consistent with a previous large VBM study of aging (Black et al., 2011), a global peak in bilateral post/precentral gyrus was observed for the negative correlation of GM with age (peak MNI=[46.50 -13.50 42]), $t_{(234)}=10.41$, Cohen's $d = 1.36$, data not shown). In addition, this same post-hoc contrast at a looser threshold ($p < 0.001$, $k=10$) was conducted in order to test whether

An additional cosinor analysis was used to test whether cyclical phenomena (cosine with annual periodicity) could explain variation in left STG GM volume. This would suggest perinatal photoperiodicity accounts for these effects (Chotai and Adolfsson, 2002; Natale et al., 2002). For this GM values were averaged across all voxels in the above left STG cluster (Figure 1A, circle), and then averaged across individuals according to birth-month (Figure 1C, “original” data). The best fit cosine waveform with annual periodicity was highly significant (amplitude=0.03, $p=4.19 \times 10^{-7}$, [0.2, 0.4] 95% CI), while the acrophase for this best fit model was -0.09 Radians (i.e. highest volumes around December 25th, and lowest volumes around June 25th). When left STG GM volumes were binned by birth day (as opposed to month), a similar and significant annual cosine effect was observed (Supplementary Figure 3).

Pattern recognition of VBM to predict SOB

A one vs. one multiclass SVM with filter feature selection, dimensionality reduction, leave-one-out cross validation, and feature selection via RFE and model selection (optimization based on number of eliminated features) using 5-fold nested cross validation was applied to the VBM data to predict participants' SOB. In females, an overall accuracy of 35% ($p=0.0006$) was achieved, while classification in males resulted in an overall accuracy of 26% ($p=0.45$). Sensitivity and specificity for each of the four seasons, Cohen's Kappa, 90% CI and Z-score are listed in Table 1.

In order to determine which pair of seasons exhibited the highest discrimination in females, a linear kernel SVM with filter feature selection, dimensionality reduction, and leave-one-out cross validation was applied to the VBM data to perform six pair-wise classifications among the four seasons. The highest discrimination was observed for winter vs. summer classification (AUC=0.71, $p<0.0005$, Figure 2). Informative voxels in this binary classification were displayed neuroanatomically. For display purposes, PCs (spatial eigenmaps) were thresholded at > 25% maximum loading factor and binarized, multiple by their SVM weight and summed (see methods for more details). In females, informative regions for winter vs. summer classification included temporal pole, middle temporal and fusiform gyrus, dorsolateral and dorsomedial prefrontal cortex, posterior cingulate, cerebellum inferior and superior parietal lobule (Figure 3). In addition, voxels that survived initial univariate filter feature selection (over the whole dataset for visualization purposes) are displayed in Supplementary Figure 4.

Note the binary SVM analyses are unbiased in that 6 models (reflecting different number of PC features used) are learned in the training sets and tested in left out samples using leave-one-out cross validation. However there is a slight positive bias in the AUCs reported in Figure 2 since a maximum from among the 6 models is chosen. Hence this AUC does not necessarily reflect the expected performance if the model were applied to new data, even if using the number of PC features that gave the maximum. However, the main motivation of this analysis is to test whether there exists information in MRI allowing significantly above chance prediction of SOB, and to determine the SOB pairs that are most distinguishable. What is important is that this positive bias is also present in the null distribution, since the maximum AUC is also chosen from among the 6 models for the randomized data (note the

mean AUC for the null distribution is above 0.50). Thus, for each pair-wise SOB comparison, the obtained non-parametric p-value is corrected for multiple comparisons across these 6 (variable number of included feature) models.

The multiclass SOB prediction constitutes two independent experiments (one in males and one in females), while the binary classifications constitute an additional 6 comparisons for a total of 8 (though not necessarily independent) comparisons (i.e. the previous 2 multiclass experiments plus all unique pair-wise SOB comparisons in only females). When applying Bonferroni correction for multiple comparisons (the most stringent form of multiple comparisons correction), the prediction results remain significant (females: multiclass $p < 0.0025$ corrected, winter vs. summer binary SVM $p < 0.01$ corrected).

Ruling out potential confounds

Race—Race was relatively evenly distributed across the four seasonal groups in both males and females (Supplementary Table 1), indicating it should not be a confound of the above effects. Nonetheless, to further investigate whether slightly disproportionate racial mixes in each season group may bias the results, an additional analysis was conducted whereby effects of race on STG grey matter volume was tested. For this a 1-way ANCOVA with 6-levels (Races listed in Supplementary Table 1) was estimated, with age, its interaction with ethnicity, scanner source and TIV as nuisance covariates. An ROI analysis of the STG revealed a marginally significant effect of race ($F=2.12$, $p=0.06$). A plot of beta estimates indicated this effect was driven by a relative decrease in STG grey matter volume among Asian or Asian British and Black or Black British participants (data not shown).

An additional analysis was conducted in which only white males were included (total $N=175$). In a whole-brain map, the global peak appeared in the STG as in the full analysis, but its significance was reduced (peak $MNI=[-58 -10 -0]$, $F=6.81$, $p<0.001$, $k=30$). A post-hoc t-test for fall/winter > spring/summer confirmed this difference in whites only ($t=3.93$, $p=0.00006$). This cluster was used to define an independent ROI to be used in the same analysis in non-whites (total $N=70$). A marginally significant effect of SOB was observed in this cluster ($F=2.49$, $p=0.07$), while the contrast fall/winter > spring/summer yielded a significant result ($t=2.45$, $p=0.009$). Furthermore, the rank order of average beta estimates across four seasons were the same, and plots were visually similar between the whites and non-whites (data not shown). Hence, although results suggest there may be an marginal effect due to race in STG grey matter volume in males, it is relatively independent of SOB and is not a confound of the SOB effect observed in STG.

Similarly, in females, there were no significant differences in the proportions of racial subgroups across season groups when combining data from all three scanners (Fisher's Exact test $p=0.84$, see Supplementary Table 1) and when combining data only from the Guys and HH scanners (Fisher's Exact Test $p=0.63$, data not shown). To further rule out a potential bias due to race, winter vs. summer classification was run within only white females from the Guys and HH scanners. This reduced the total female winter and summer sample size by ~20% ($N_{\text{whites}}+N_{\text{non-whites}}=137$, $N_{\text{whites}}=108$) with $N_{\text{win}}=50$ and $N_{\text{sum}}=58$. Discrimination was slightly reduced relative to discrimination achieved when combining white and non-white female participants, but still remained significantly higher than chance

(AUC=0.65, $p=0.004$). The above results confirm race does not account for winter vs. summer discrimination observed in females.

Relative age effect and scholastic experience—Previous studies have suggested higher grey matter volume in superior temporal gyrus is associated with more years of education (Arenaza-Urquijo et al., 2013). Recent studies have suggested that date of birth impacts cognitive and educational outcomes, which might thus account for the observed SOB effects in STG. The effect of birth-date on educational outcome has been attributed to differences in age at start of school, which, depending on the country, is often determined by a single cutoff date. In England, the school year begins September 1st, so those born in the summer are typically youngest in their class, while those born just after September 1st are the oldest. Data from a Norwegian sample suggest a negative effect of starting school at an older age (Black et al., 2011), while data from a large cohort in England suggest that summer born (i.e. August) children, who are youngest in their academic year, perform worse than those born after September 1st, who are oldest in their academic year (Crawford et al., 2007; 2010).

Evidence for a relative age effect in left STG GM volume, which would consist of a line with a sharp drop between two consecutive months (http://en.wikipedia.org/wiki/Relative_age_effect), was not observed. Instead, a plot of average left STG volumes in males according to birth month significantly followed an annually periodic cosine pattern, with a peak amplitude towards end of December and nadir towards the end of June (zero amplitude test: $p<5\times10^{-7}$, Figure 1C). This annual cosine pattern (i.e. peak towards end of December, nadir towards end of June) is very similar to that found for morning/eveningness preference (Natale et al., 2002) and for the dopamine metabolite homovanillic acid (HVA), considering an indirect indicator of dopamine turnover rate (Chotai and Adolfsson, 2002). These results suggest the observed effect is due to differences in perinatal photoperiod, which also follows this annual cosine pattern.

In addition, scholastic experience was investigated. The number of years of education (here quantified with the demographic variable “Qualification”, see Supplementary Table 1 for category definitions) was relatively evenly distributed across the four season groups (Fisher Exact Test $p=0.62$ in males, $p=0.23$ in females), indicating it should not confound the observed results in the left STG. Nonetheless, further analyses were conducted to rule education as a potential confound. A 2nd level ANCOVA model was constructed as above (see methods), but included an additional covariate for Qualification. Using the cluster in the left STG (shown in Figure 1), an ROI analysis revealed no effect of Qualification ($t=0.05$, $p=0.48$). Furthermore, the peak F-value for the SOB effects in the STG was not affected ($F=11.58$, $p=0.009$ FWE) when Qualification was included as a covariate in the model. Similarly, in females, when features were adjusted for the effects of Qualification prior to winter vs. summer classification, peak discrimination remained at AUC=0.71.

Discussion

This study demonstrates and identifies SOB effects in the adult human brain, and shows that MRI carries information when predicting individual SOB. These results imply that

environmental variables associated with SOB impact human brain development, which subsequently exerts influences on brain structure that persist through adulthood. These effects may mediate previously observed SOB associations with prevalence of neurobehavioral disorders and personality traits. The strongest overall effect of SOB was observed in males in the left STG, which exhibited reduced GM volume in spring/summer relative to fall/winter births. In the current data, this SOB effect size was sizeable (Cohen's $d=0.68$) compared to the well-known effect of aging on GM volume (Cohen's $d=1.36$). The causality of SOB on GM volume is assumed primarily because of temporal precedence (i.e. one is born before adult GM volume is established). In addition, it is unlikely that knowledge of one's birth season could influence his/her behavior and subsequently his/her brain structure. That GM volume in the left STG follows an annual periodicity suggests that perinatal photoperiod exerts a lasting and causal impact on the gross morphology of this region.

Superior temporal gyrus contains auditory cortex and has specialized functions for human language and social cognition (Bigler et al., 2007). A genome-wide analysis study identified ~350 genes that are differentially expressed in this specialized region, relative to the rest of cortex, during human midgestation (Abrahams et al., 2007). The current results suggest that developmental gene $\times$ environment interactions, possibly via perinatal photoperiod effects on circadian clock genes in the suprachiasmatic nuclei and elsewhere (Ciarleglio et al., 2011), influence developmental patterning of the STG, ultimately resulting in gross morphological differences of this region.

In general, associations of season of birth with behavioral traits rely on large sample sizes because the effect size is relatively small. For instance, in a sample of 2,282 females, the effect size of novelty seeking (summer female births > winter female births) was $d \sim 0.13$ (Chotai et al., 2009b). By comparison studies comparing grey matter volumes between healthy controls and patients with schizophrenia (about 20 subjects each group) have reported effect sizes (Cohen's d) greater than 1 (Kuroki et al., 2006). Thus one would anticipate a greater proportion of variance explained when including brain volume as an intermediate phenotype between SOB and behavior.

Interestingly, reduced grey matter volume of left STG has been a consistently replicated neuroanatomical feature of schizophrenia (Dickey et al., 1999; Honea et al., 2005), while 5-8% winter/spring excess of births has been associated with higher prevalence of schizophrenia in the Northern hemisphere (Davies et al., 2003; Torrey et al., 1997). Although here reduced left STG grey matter volume was observed for spring/summer births in a healthy adult population, based on the observation that both SOB and schizophrenia predict left STG volume, one might speculate this region mediates SOB effects on schizophrenia in a male clinical population. Higher suicide rates in spring/summer vs. fall/winter births have also been consistently observed (Salib and Cortina-Borja, 2006; Woo et al., 2012), while reduced STG volume has been previously observed in suicidal depression vs. non-suicidal depression (Hwang et al., 2010), and in schizophrenic subjects who had attempted suicide vs. not (Aguilar et al., 2008). I speculate that neuroimaging, and in particular STG grey matter volume, could be a valuable intermediate-phenotype (Meyer-Lindenberg and Weinberger, 2006) in bridging the gap between SOB and risk for

schizophrenia and suicidality. While the current study demonstrates a SOB effect on neuroanatomical structure in healthy participants, future studies using large clinical datasets could directly test whether neuroimaging-based phenotypes mediate SOB effects on risk for these neurobehavioral disorders.

In the current neuroimaging study, SOB effects emerged only when analyses were conducted separately in males and females. This is consistent with many previous association studies which show sexually dimorphic effects: for example SOB was shown to preferentially modulate morning-evening preference in males (Natale and Adan, 1999) while other studies have associated female winter-births with lower novelty seeking in adults (Chotai et al., 2009b) and male winter-births with higher novelty and sensation-seeking traits (Eisenberg et al., 2007). There are several reasons that could explain why the significant prediction of SOB using MRI only emerged in females: 1) Effects of SOB on the adult brain are sexually dimorphic, consistent with previous birth-season epidemiology literature. These effects on the adult brain may manifest in a more local manner in males (detectable with univariate approach) but in a more distributed manner in females (detectable with multivariate pattern recognition) 2) The distributed effect of SOB in males is more subtle than the effects in females. In this case, the current analysis and/or data acquisition was not sensitive enough to detect distributed SOB effects in males. Higher field strength scanners, more sensitive analysis (i.e. different kernel, regularization parameter, type of multiclass machine, etc. used for the SVM), and/or more subjects in future studies may yield positive results 3) It is possible that, among the males, there was a higher proportion of participants who had immigrated from the Southern Hemisphere, where seasons are opposite to those in the Northern Hemisphere. This would have diluted the main effect of birth-season and caused a Type 2 error (i.e. a false negative, please see limitations section).

The peak left STG coordinate in males (Figure 1A) was not included in the informative feature set for predicting SOB in females (Figure 3). However, inspection of Supplementary Figure 3 (3rd row, leftmost axial slice) shows nearby voxels in bilateral STG which show an opposite (though non-significant) tendency of greater volume in summer vs. winter births in females (i.e. all voxels in bilateral STG are yellow). To further facilitate comparison of SOB effects on bilateral STG between males and females, I first examined whether right STG exhibited similar SOB effects as left STG in males. A looser threshold ($p < 0.001$, $k = 10$) for the contrast fall/winter > spring/summer revealed a sub-threshold effect in right STG, suggesting that SOB effects on STG in males are indeed bilateral and in the same direction (right STG, peak MNI=[49 -19 10], $t = 4.54$, $p = 0.058$ FWE, Supplemental Figure 5). A liberal threshold ($p < 0.1$ uncorrected) in the SPM analysis for females confirmed a tendency for greater GM volume (summer > winter) in the same peak left STG coordinate that showed greater fall/winter > summer/spring volumes in males (left STG, MNI=[-58 -9 0], $t = 1.61$, data not shown). Although provisional, these observations suggest that SOB exerts opposite, if not preferential, effects on bilateral STG in males relative to females.

Personality traits such as novelty seeking have been associated with substance abuse, and may also mediate dopamine-related genetic influences on substance dependence (Erren et al., 2012). Other lines of research propose that SOB modifies the behavioral expression of dopaminergic genetic polymorphisms on novelty and sensation seeking behavior (Roussos et

al., 2010; Eisenberg et al., 2007), while both dopaminergic genetic polymorphisms (Caldu et al., 2007) and novelty seeking (Gardini et al., 2009) have been associated with differences in brain structure and function. Thus, future studies that assess SOB, personality traits, genetics, and neuroimaging all within the same individuals could further elucidate the role each of these factors play in determining behavior, cognitive outcome and risk and/or resilience for substance dependence and other psychiatric disorders.

Unfortunately, birthday data is currently considered protected health information (PHI) which is required to be de-identified under the current Health Insurance Portability and Accountability Act (HIPAA) guidelines (<http://healthcare.partners.org/phsirb/hipaaov.htm>). However, the current results suggest important benefits in making birthdate (as well as birthplace, since seasonal photoperiod varies according to latitude) available to researchers who utilize large-scale, open source neuroimaging repositories such as the Human Connectome Project (<http://www.humanconnectomeproject.org/>) and the International Data Sharing Initiative (INDI) repository of resting fMRI data (http://fcon_1000.projects.nitrc.org/indi/summerofsharing2012.html). This would allow the combined analysis of SOB, neuroimaging phenotypes and personality and behavioral traits related to neurobehavioral disorders such as schizophrenia, substance dependence, depression, bipolar disorder, anxiety and autism, and hence further the refinement and discovery of new etiological risk models for mental disorder.

Limitations

Season of birth effects have been shown to be greater at higher latitudes (Davies et al., 2003), consistent with the hypothesis that perinatal photoperiod primarily accounts for these effects (Ciarleglio et al., 2011). Thus, a primary limitation of the current work is that participants' birth place information was not recorded. However, this limitation would only increase the risk for a Type 2 error (i.e. increased chance of a false negative), not a Type 1 error (i.e. increased chance of a false positive). In the most likely scenario, there is a small to medium percentage of participants from the Southern Hemisphere evenly distributed across the four season groups. This would only dilute the signal, not generate a false positive. In other, less likely, scenarios, one or more of the season groups contained a disproportionate number of participants from the Southern Hemisphere, or the all groups contained a majority of participants born in the Southern Hemisphere. This would compromise the directionality of the results (i.e. there is really greater STG volumes in spring/summer, not fall/winter), and not the main conclusion of this study: that season of birth in adult humans is detectable with MRI. In all the above hypothetical cases, it is still season of birth (regardless of the actual season label) that is driving the effects observed here. Future studies should assess participants' place of birth and/or maternal location during pregnancy in order to allow more sensitive and refined analyses of phenotypes associated with perinatal photoperiod (Erren et al., 2012).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Abrahams BS, Tentler D, Perederiy JV, Oldham MC, Coppola G, Geschwind DH. Genome-wide analyses of human perisylvian cerebral cortical patterning. *Proc Natl Acad Sci U S A*. 2007; 104:17849–54. [PubMed: 17978184]
- Aguilar EJ, García-Martí G, Martí-Bonmatí L, Lull JJ, Moratal D, Escartí MJ, Robles M, González JC, Guillamón MI, Sanjuán J. Left orbitofrontal and superior temporal gyrus structural changes associated to suicidal behavior in patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008; 32:1673–6. [PubMed: 18657587]
- Arenaza-Urquijo EM, Landeau B, La Joie R, Mevel K, Mézenge F, Perrotin A, Desgranges B, Bartrés-Faz D, Eustache F, Chételat G. Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders. *Neuroimage*. 2013
- Ashburner J, Friston KJ. Unified segmentation. *NeuroImage*. 2005; 26:839–851. [PubMed: 15955494]
- Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage*. 2000; 11:805–21. [PubMed: 10860804]
- Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage*. 2007; 38:95–113. [PubMed: 17761438]
- Bersani G, Pucci D, Gherardelli S, Conforti F, Bersani I, Osborn JF, Hansen V, Pancheri P. Excess in the spring and deficit in the autumn in birth rates of male schizophrenic patients in Italy: potential role of perinatal risk factors. *J Matern Fetal Neonatal Med*. 2006; 19:425–31. [PubMed: 16923698]
- Bigler ED, Mortensen S, Neeley ES, Ozonoff S, Krasny L, Johnson M, Lu J, Provencal SL, McMahon W, Lainhart JE. Superior temporal gyrus, language function, and autism. *Dev Neuropsychol*. 2007; 31:217–38. [PubMed: 17488217]
- Black SE, Devereux PJ, Salvanes KG. Too young to leave the nest? The effects of school starting age. *The Review of Economics and Statistics*. 2011; 93:455–467.
- Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol*. 2011; 93:23–58. [PubMed: 20955757]
- Castrogiovanni P, Iapichino S, Pacchierotti C, Pieraccini F. Season of birth in panic disorder. *Neuropsychobiology*. 1999; 40:177–82. [PubMed: 10559699]
- Chotai J, Joukamaa M, Taanila A, Lichtermann D, Miettunen J. Novelty seeking among adult women is lower for the winter borns compared to the summer borns: replication in a large Finnish birth cohort. *Compr Psychiatry*. 2009a; 50:562–6. [PubMed: 19840595]
- Chotai J, Joukamaa M, Taanila A, Lichtermann D, Miettunen J. Novelty seeking among adult women is lower for the winter borns compared to the summer borns: replication in a large Finnish birth cohort. *Compr Psychiatry*. 2009b; 50:562–6. [PubMed: 19840595]
- Chotai J, Adolfsson R. Converging evidence suggests that monoamine neurotransmitter turnover in human adults is associated with their season of birth. *Eur Arch Psychiatry Clin Neurosci*. 2002; 252:130–4. [PubMed: 12192471]
- Chotai J, Asberg M. Variations in CSF monoamine metabolites according to the season of birth. *Neuropsychobiology*. 1999; 39:57–62. [PubMed: 10072660]
- Ciarleglio CM, Axley JC, Strauss BR, Gamble KL, McMahon DG. Perinatal photoperiod imprints the circadian clock. *Nat Neurosci*. 2011; 14:25–7. [PubMed: 21131951]
- Cohen AS, Najolia GM. Birth characteristics and schizotypy: evidence of a potential “second hit”. *J Psychiatr Res*. 2011; 45:955–61. [PubMed: 21208628]
- Cohen J. A coefficient of agreement for nominal scales. *Educational and psychological measurement*. 1960; 20:37.

- Congalton, RG.; Green, K. Assessing the accuracy of remotely sensed data: principles and practices. Boca Raton, FL: CRC Press; 2008.
- Crawford, C.; Dearden, L.; Meghir, C. When you are born matters: The impact of date of birth on child cognitive outcomes in England. London, England: Centre for the Economics of Education; 2007.
- Crawford C, Dearden L, Meghir C. When you are born matters: the impact of date of birth on educational outcomes in England. IFS Working Papers. 2010; 10:06.
- Davatzikos C. Why voxel-based morphometric analysis should be used with great caution when characterizing group differences. *Neuroimage*. 2004; 23:17–20. [PubMed: 15325347]
- Davies G, Welham J, Chant D, Torrey EF, McGrath J. A systematic review and meta-analysis of Northern Hemisphere season of birth studies in schizophrenia. *Schizophr Bull*. 2003; 29:587–93. [PubMed: 14609251]
- Dickey CC, McCarley RW, Voglmaier MM, Niznikiewicz MA, Seidman LJ, Hirayasu Y, Fischer I, Teh EK, Van Rhoads R, Jakab M, et al. Schizotypal personality disorder and MRI abnormalities of temporal lobe gray matter. *Biol Psychiatry*. 1999; 45:1393–402. [PubMed: 10356620]
- Doblhammer G, Vaupel JW. Lifespan depends on month of birth. *Proc Natl Acad Sci U S A*. 2001; 98:2934–9. [PubMed: 11226344]
- Eisenberg DT, Campbell B, Mackillop J, Lum JK, Wilson DS. Season of birth and dopamine receptor gene associations with impulsivity, sensation seeking and reproductive behaviors. *PLoS ONE*. 2007; 2:e1216. [PubMed: 18030347]
- Erren TC, Koch MS, Gross JV, Reiter RJ, Meyer-Rochow VB. A possible role of perinatal light in mood disorders and internal cancers: reconciliation of instability and latitude concepts. *Neuro Endocrinol Lett*. 2012; 33:314–7. [PubMed: 22635091]
- Franke K, Ziegler G, Klöppel S, Gaser C. Alzheimer's Disease Neuroimaging Initiative. Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: exploring the influence of various parameters. *Neuroimage*. 2010; 50:883–92. [PubMed: 20070949]
- Grytten N, Torkildsen O, Aarseth JH, Benjaminsen E, Celius EG, Dahl OP, Holmøy T, Løken-Amsrud K, Midgard R, Myhr KM, et al. Month of birth as a latitude-dependent risk factor for multiple sclerosis in Norway. *Mult Scler*. 2013; 19:1028–34. [PubMed: 23257620]
- Guyon I, Weston J, Barnhill S, Vapnik V. Gene selection for cancer classification using support vector machines. *Machine learning*. 2002; 46:389–422.
- Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982; 143:29–36. [PubMed: 7063747]
- Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE. Nonstationary cluster-size inference with random field and permutation methods. *Neuroimage*. 2004; 22:676–87. [PubMed: 15193596]
- Henley SM, Ridgway GR, Scallan RI, Klöppel S, Tabrizi SJ, Fox NC, Kassubek J. EHDN Imaging Working Group. Pitfalls in the use of voxel-based morphometry as a biomarker: examples from huntington disease. *AJNR Am J Neuroradiol*. 2010; 31:711–9. [PubMed: 20037137]
- Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005; 162:2233–45. [PubMed: 16330585]
- Hori H, Teraishi T, Sasayama D, Matsuo J, Kawamoto Y, Kinoshita Y, Kunugi H. Relationships between season of birth, schizotypy, temperament, character and neurocognition in a non-clinical population. *Psychiatry Res*. 2012a; 195:69–75. [PubMed: 21824667]
- Hori H, Teraishi T, Sasayama D, Matsuo J, Kawamoto Y, Kinoshita Y, Kunugi H. Relationships between season of birth, schizotypy, temperament, character and neurocognition in a non-clinical population. *Psychiatry Res*. 2012b; 195:69–75. [PubMed: 21824667]
- Hwang JP, Lee TW, Tsai SJ, Chen TJ, Yang CH, Lirng JF, Tsai CF. Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. *J Geriatr Psychiatry Neurol*. 2010; 23:171–84. [PubMed: 20430976]
- Jongbloet PH, Groenewoud HM, Roelvelde N. Seasonally bound ovopathy versus “temperature at conception” as cause for anorexia nervosa and other eating disorders. *Int J Eat Disord*. 2005; 38:236–43. [PubMed: 16211635]
- Kaludjerovic J, Vieth R. Relationship between vitamin D during perinatal development and health. *J Midwifery Womens Health*. 2010; 55:550–60. [PubMed: 20974417]

- Kuroki N, Shenton ME, Salisbury DF, Hirayasu Y, Onitsuka T, Ersner-Hersfield H, Yurgelun-Todd D, Kikinis R, Jolesz FA, McCarley RW. Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. *Am J Psychiatry*. 2006; 163:2103–10. [PubMed: 17151161]
- Lao Z, Shen D, Xue Z, Karacali B, Resnick SM, Davatzikos C. Morphological classification of brains via high-dimensional shape transformations and machine learning methods. *Neuroimage*. 2004; 21:46–57. [PubMed: 14741641]
- Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nature reviews Neuroscience*. 2006; 7:818–827. [PubMed: 16988657]
- Mikl M, Marecek R, Hlustík P, Pavlicová M, Drastich A, Chlebus P, Brázdil M, Krupa P. Effects of spatial smoothing on fMRI group inferences. *Magn Reson Imaging*. 2008; 26:490–503. [PubMed: 18060720]
- Natale V, Adan A, Chotai J. Further results on the association between morningness-eveningness preference and the season of birth in human adults. *Neuropsychobiology*. 2002; 46:209–14. [PubMed: 12566940]
- Natale V, Adan A, Fabbri M. Season of birth, gender, and social-cultural effects on sleep timing preferences in humans. *Sleep*. 2009; 32:423–6. [PubMed: 19294963]
- Natale V, Adan A. Season of birth modulates morningness-eveningness preference in humans. *Neurosci Lett*. 1999; 274:139–41. [PubMed: 10553957]
- Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinor-rhythmometry. *Chronobiologia*. 1979; 6:305–23. [PubMed: 548245]
- Reid HM, Zborowski MJ. Schizophrenia-proneness, season of birth and sleep: Elevated schizotypy scores are associated with spring births and extremes of sleep. *Personality and individual differences*. 2006; 41:1185–1193.
- Roussos P, Giakoumaki SG, Bitsios P. Cognitive and emotional processing associated with the Season of Birth and dopamine D4 receptor gene. *Neuropsychologia*. 2010; 48:3926–33. [PubMed: 20875435]
- Salib E, Cortina-Borja M. Effect of month of birth on the risk of suicide. *Br J Psychiatry*. 2006; 188:416–22. [PubMed: 16648527]
- Schwartz PJ. Season of birth in schizophrenia: a maternal-fetal chronobiological hypothesis. *Med Hypotheses*. 2011; 76:785–93. [PubMed: 21382670]
- Shokouhi M, Barnes A, Suckling J, Moorhead TW, Brennan D, Job D, Lymer K, Dazzan P, Reis Marques T, Mackay C, et al. Assessment of the impact of the scanner-related factors on brain morphometry analysis with Brainvisa. *BMC Med Imaging*. 2011; 11:23. [PubMed: 22189342]
- Tonetti L, Fabbri M, Martoni M, Natale V. Season of birth and mood seasonality in late childhood and adolescence. *Psychiatry Res*. 2012; 195:66–8. [PubMed: 21840608]
- Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr Res*. 1997; 28:1–38. [PubMed: 9428062]
- Vapnik VN. An overview of statistical learning theory. *IEEE transactions on neural networks / a publication of the IEEE Neural Networks Council*. 1999; 10:988–999. [PubMed: 18252602]
- Woo JM, Okusaga O, Postolache TT. Seasonality of suicidal behavior. *Int J Environ Res Public Health*. 2012; 9:531–47. [PubMed: 22470308]

Highlights

- Season of birth (SOB) in adult humans is detectable with brain MRI
- In males, SOB modulates left superior temporal gyrus (STG) volume
- In males, left STG volume shows annual periodicity, with peak/nadir in December /June
- In females, MRI has information allowing above chance prediction of individual SOB
- In females, winter vs. summer births are most distinguishable with MRI

Fig. 1. SOB effects on regional grey matter volume

(A) Standard univariate SPM analysis revealed a significant SOB effect in left superior temporal gyrus in males (left STG, cluster size=35, peak MNI [-58 -9 0], $F=11.64$, $p=0.009$ FWE corrected). Whole brain statistical map was thresholded at $p<0.05$ FWE corrected. (B) A plot of beta estimates at peak coordinate across the four seasons shows this effect is driven by greater grey matter volume in winter and fall births. Error bars represent 90% CI. (C) Average left STG grey matter volumes in each birth month (left to right, January through December, "Original"). Cosinor analysis (see methods) revealed a significant cyclic effect with period of 12 months (zero amplitude test: $p=4.19 \times 10^{-7}$) suggesting perinatal photoperiod accounts for SOB effect observed in left STG. (D) Point estimates for amplitude (i.e. half the distance between peaks of the fitted waveform = 0.03, y-axis) and acrophase (i.e. timepoint in the cycle of highest amplitude relative to January = -0.09 Radians) indicated by solid black line, with 95% joint confidence intervals (circle).

Fig. 2. Pattern recognition of regional grey matter volume to predict SOB

(A) In females, classification was highest when predicting winter vs. summer (AUC=0.71, $p < 0.0005$). Maximum discrimination was achieved when using PCs that explained 95% of the total variance among initially filtered features (see methods). Error bars represent 90% CI.

Fig. 3. Informative brain regions when predicting winter vs. summer SOB

In females, informative voxels included temporal pole ($z=-36,-24$), fusiform cortex ($z=-24$), middle occipital cortex and insula ($z=12$), precuneus ($z=24$), parietal lobe, and dorsomedial and dorsolateral prefrontal cortex ($z=36,48$). For display purposes, filter feature selection (top 10% by absolute t-score) was applied to the full dataset, and 69 PCs that explained 90% of the total variance were thresholded at $> 25\%$ maximum loading factor in the spatial eigenmap, binarized, and multiplied by the SVM weight for that PC (when training over the full dataset). These binarized, SVM weighted PC maps were then summed, and each voxel was color coded according to its sum total weight score. For displays of the top 10% features (initial feature selection) see supplementary figures 3.

Table 1

Results from multiclass season of birth classification in males and females.

Females	<i>Winter</i>	<i>Spring</i>	<i>Summer</i>	<i>Fall</i>
<i>Sensitivity</i>	0.42	0.31	0.4	0.25
<i>Specificity</i>	0.83	0.76	0.75	0.78
<i>Overall accuracy</i>	<i>Cohen's K</i>	<i>K 90% CI</i>	<i>Z-score</i>	<i>P-value</i>
0.35	0.13	0.20 0.05	3.24	0.0006
Males	<i>Winter</i>	<i>Spring</i>	<i>Summer</i>	<i>Fall</i>
<i>Sensitivity</i>	0.22	0.20	0.29	0.31
<i>Specificity</i>	0.77	0.8	0.74	0.7
<i>Overall accuracy</i>	<i>Cohen's K</i>	<i>K 90% CI</i>	<i>Z-score</i>	<i>P-value</i>
0.26	0.005	0.08 -0.07	0.13	0.45