Seasonality in human cognitive brain responses

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Daily variations in the environment have shaped life on Earth, with circadian cycles identified in most living organisms. Likewise, seasons correspond to annual environmental fluctuations to which organisms have adapted. However, little is known about seasonal variations in human brain physiology. We investigated annual rhythms of brain activity in a cross-sectional study of healthy young participants. They were maintained in an environment free of seasonal cues for 4.5 d, after which brain responses were assessed using functional magnetic resonance imaging (fMRI) while they performed two different cognitive tasks. Brain responses to both tasks varied significantly across seasons, but the phase of these annual rhythms was strikingly different, speaking for a complex impact of season on human brain function. For the sustained attention task, the maximum and minimum responses were located around summer and winter solstices, respectively, whereas for the working memory task, maximum and minimum responses were observed around autumn and spring equinoxes. These findings reveal previously unappreciated process-specific seasonality in human cognitive brain function that could contribute to intra-individual cognitive changes at specific times of year and changes in affective control in vulnerable populations.

season | cognition | fMRI | annual | attention

Daily variations in the environment have constrained life on Earth, with circadian cycles identified in most living organisms, including in human physiology and cognition (1, 2). Seasonal variations in the environment have also triggered annual adaptations that are observed in the majority of species (for a review, see ref. 1). However, seasonal variations may seem more limited in our species or they are at least less recognized (3). Seasonality has indeed been reported for several physiological aspects including blood pressure (4), cholesterol (5), or calorie intake (6), with higher levels seen in winter or fall for food intake. Recently, seasonal variation in expression levels of a large set of genes has been reported for human white blood cells and adipose tissue (7). Furthermore, seasonal variations have been observed in several behavioral dimensions with peaks occurring at different time of year depending on the variable considered: conception (winter/spring peak) and death [winter peak (8)] or violent suicide [spring/summer peak (9)]. Mood has been the most extensively studied aspect of human behavior, with a large portion of the general population undergoing seasonal deteriorations in mood in winter, but these do not reach clinical threshold [e.g., subsyndromal seasonal affective disorder: up to 18% in North America (10)]. Furthermore, sparse studies suggest that, in addition to mood, other cognitive brain functions show annual variations in healthy individuals, but results are not consistent (11–13).

Animal research suggests that the suprachiasmatic nucleus, site of the master circadian clock, is at least one of the sites mediating annual rhythmicity (14). The well-characterized circadian genetic machinery is also implicated in tracking seasonal changes (15). It is therefore likely that seasonality in human species involves the circadian timing system and that the previously identified brain correlates of the circadian variations in cognitive brain function (2) play a role in annual changes in human cognition. Although seasonal changes in photoperiod together with neurotransmitters and neurotrophic factors seem to mediate seasonal mood variation in humans (16–20), the brain bases of seasonality in human cognition remain elusive. This lack of evidence arises in part from the fact that genuine seasonal rhythms of human brain function are difficult to measure. A number of factors that could directly affect brain function have indeed to be controlled: light exposure, sleep/wake rhythm, external temperature, food intake, physical exercise, and social interactions.

Here, we took advantage of a study completed in our laboratory under strictly controlled conditions, devoid of seasonal cues for 4.5 d, to assess annual rhythms in human cognitive brain function. The primary goal of the study was to assess the neural correlates of two tasks probing different cognitive domains during total sleep deprivation. Because the enrollment of participant was carefully timed such that the assessments would span all seasons, annual variations in the neural responses (assessed after recovery from the sleep deprivation) could be assessed. We hypothesized that, following 4.5 d under controlled conditions, brain responses to both tasks would undergo seasonal variations with higher and lower responses, respectively, around summer and winter solstices. In line with previous observations (13), we further postulated that annual variations would be more evident in the more basic attentional task compared with the more complex, higher-order executive task.

Significance

Evidence for seasonality in humans is limited. Mood probably stands as the aspect of human brain function most acknowledged as being affected by season. Yet, the present study provides compelling evidence for previously unappreciated annual variations in the cerebral activity required to sustain ongoing cognitive processes in healthy volunteers. The data further show that this annual rhythmicity is cognitive-process-specific (i.e., the phase of the rhythm changes between cognitive tasks), speaking for a complex impact of season on human brain function. Annual variations in cognitive brain function may contribute to explain intraindividual cognitive changes that could emerge at specific times of year.

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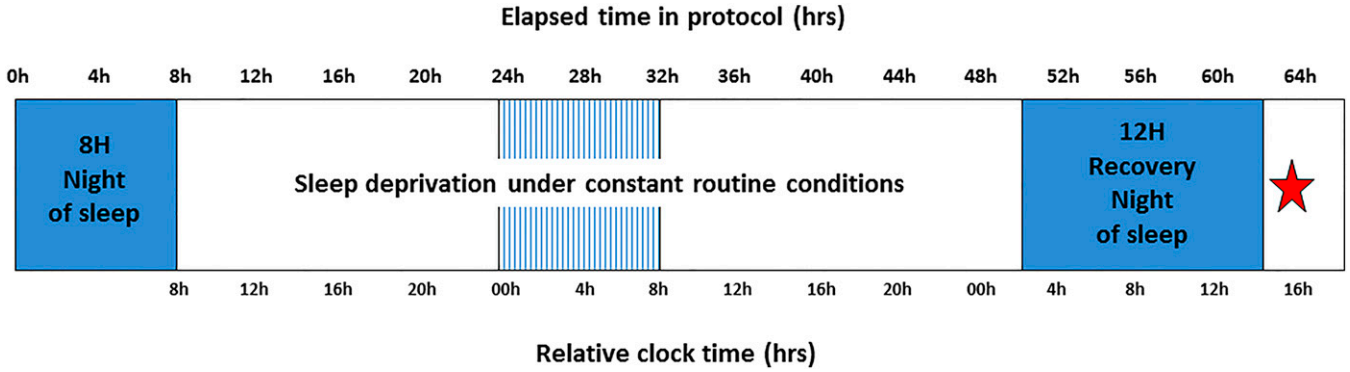

Fig. 1. Schematic representation of the protocol. Following an 8-h baseline night of sleep in complete darkness, participants underwent a 42-h sleep deprivation under constant routine conditions in dim light (<5 lx, 19 °C, semirecumbent position, regular liquid isocaloric food intake, no time cues, sound-proofed room). They were then given a 12-h recovery sleep opportunity in darkness, an hour after which they completed fMRI recordings (red star). Functional MRI recordings were completed while lying down in darkness and included PVT and n-back tasks. Relative clock time for participants habitually waking up at 8:00 AM. Striped blue box during sleep deprivation represents the habitual sleep period. The figure represents the last ~2.5 d of the protocol; see Fig. S1 for a description of the entire in-laboratory experiment.

Results and Discussion

Twenty-eight young, healthy participants [age 21 ± 1.5 y (mean ± SD); 14 women; Table S1] took part in a cross-sectional study conducted in Liège (Belgium, latitude 50.633° N, longitude 5.567° E), between May 2010 and October 2011. They were instructed to follow a regular sleep/wake schedule for 3 wk before a 4.5-d

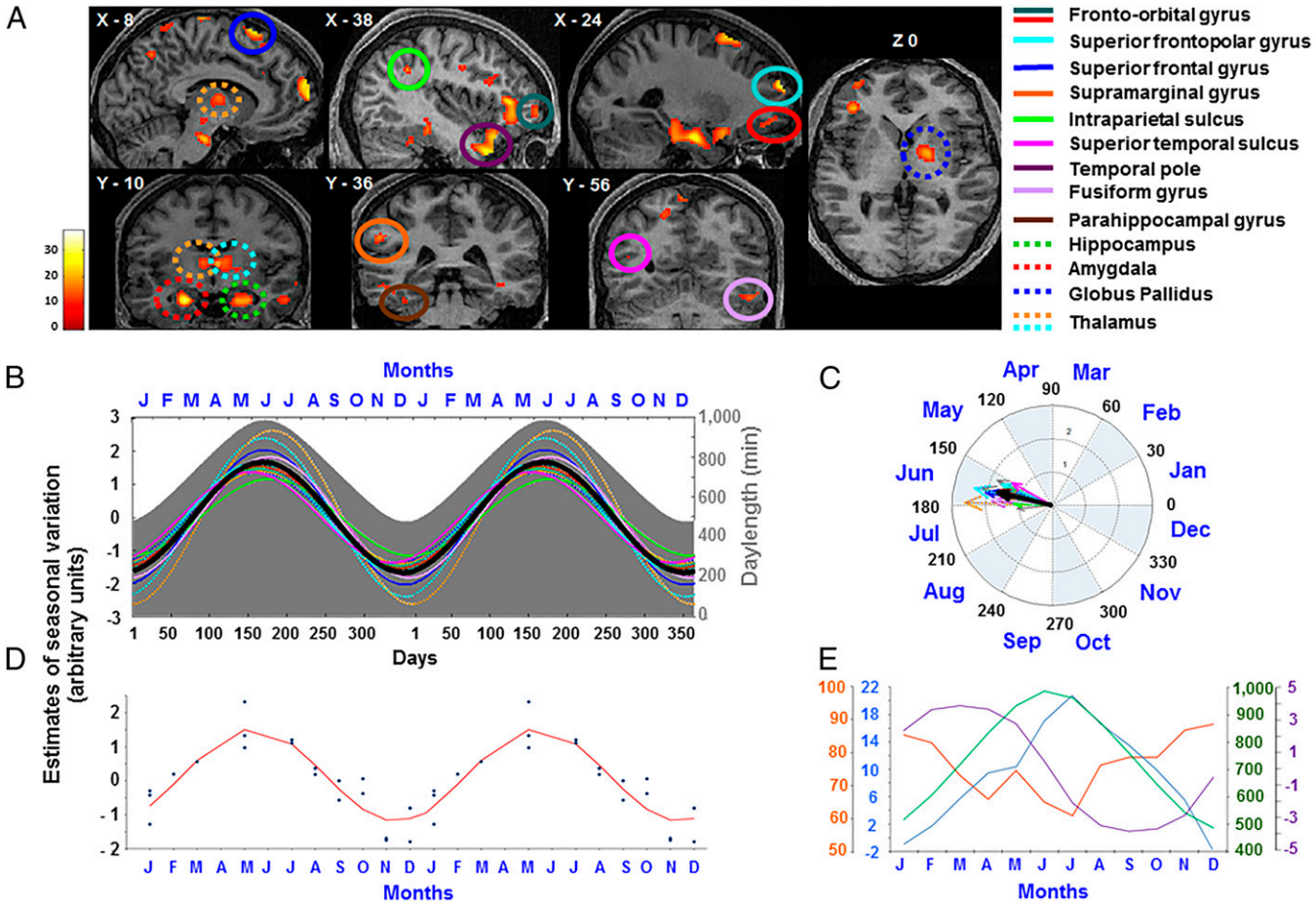

Fig. 2. Seasonal variations in brain activity associated with sustained attention. (*A*) Significant ($p_{corrected} < 0.05$) seasonal variations in PVT brain responses displayed over the mean structural image of all participants (display at $p_{uncorrected} < 0.001$). Only clusters >30 voxels are displayed (see Table 1 for full results). Vertical color bar corresponds to *F*-test values (*B*) Double plot of PVT brain response estimates in regions of *A* in a sinusoidal representation. Day 1 corresponds to January 1. First letter of each month is displayed on top. Thick black line corresponds to average of all response estimates. Gray area represents daily da ylength (in minutes) in Liège. (*C*) Same as *B* in polar coordinates; arrow length represents seasonal variation amplitude. One degree is roughly equal to 1 d (360° for 365 d). Maximum responses were located between 152° and 188° (mean 168.9) (i.e., June 3 and July 9) (mean June 20). (*D*) Double plot of individual activity estimates in a representative region of *A* (amygdala) and its sinusoidal fit (red line). (*E*) Seasonal environmental factors recorded in Liège in 2011: temperature (Celsius degrees, blue), humidity (percent, red), day length (minutes, green), and day-to-day day-length gain/loss (minutes, violet).

Table 1. Seasonal variation in PVT brain responses

Brain areas	Side	X Y Z	Z score	*P* value
Frontoorbital gyrus	L	−38 54 −6	3.43	0.017
	L	−26 52 −10	3.56	0.012
Medial frontoorbital gyrus	R	10 56 −12	3.34	0.022
Superior frontopolar gyrus	L	−26 60 20	4.32	<0.01*
Superior frontal gyrus	L	−14 20 64	4.56	<0.01*
Middle frontal gyrus	L	−50 18 38	3.29	0.025
Pre-SMA	R	2 20 48	3.11	0.042
Posterior cingulate gyrus	L	−4 −42 22	3.10	0.042
Precuneus	L	−18 −50 36	3.50	0.014
Supramarginal gyrus	L	−56 −36 30	3.93	0.004
Intraparietal sulcus	L	−30 −46 34	3.29	0.025
	R	30 −42 36	3.37	0.021
Superior temporal sulcus	L	−48 −58 16	3.45	0.016
Temporal pole	L	−38 16 −36	4.66	<0.05*
Fusiform gyrus	R	50 −56 −20	3.74	0.007
	R	42 −58 −18	3.12	0.039
Parahippocampal gyrus	L	−32 −28 -24	4.61	<0.05*
Hippocampus	R	28 −14 -24	4.58	<0.05*
Caudate nucleus	L	−6 4 −4	3.23	0.030
Amygdala	L	−22 −10 −24	4.87	<0.05*
Globus pallidus	R	18 −2 0	4.21	0.001
Thalamus	R	10 −6 8	3.86	0.005
	L	−8 −8 10	3.79	0.006

P values corrected for multiple comparisons over a priori small volume of interests, except *corrected over the entire brain. X Y Z: coordinates (millimeters) in Montreal Neurological Institute stereotactic space. All regions survived to an inclusive mask ($p_{uncorrected}$ = 0.001) consisting of a brain map of the potential PVT brain responses covarying with day length, suggesting that annual variations in all regions are significantly driven by the seasonal changes in day length. No region survived to an inclusive mask ($p_{uncorrected}$ = 0.001), whereas all regions survived exclusive masking ($p_{uncorrected}$ < 0.05) with a brain map of the potential executive brain responses covarying (*i*) subjective mood and (*ii*) PVT performance (median, 20% fastest, 20% slowest reaction times), suggesting that annual variations in all regions are not significantly driven by the seasonal changes in these variables. L, left; R, right.

in-laboratory protocol devoid of seasonal cues (Figs. S1 and S2). Functional MRI (fMRI) recordings were acquired 1 h after wake-up time, following 63 h of strictly controlled experimental conditions (Fig. 1). Each recording included a sustained attention task [visual psychomotor vigilance task, PVT (21)], and a higher-order executive function task [auditory n-back task, involving storage, updating, and comparison of information in working memory (22)].

We first focused on the brain responses induced by the PVT and found significant annual variations in areas involved in alertness [thalamus (23) and amygdala (24)] and in executive control [frontal areas (25) and hippocampus (26)] (Fig. 2*A* and Table 1). Seasonal variations were also detected in the globus pallidus, parahippocampal gyrus, fusiform gyrus, supramarginal gyrus, and in the temporal pole recruited during PVT execution (27, 28) and in the precuneus involved in visuospatial attention (29). As postulated, extraction of the seasonal variations in PVT brain responses revealed a similar rhythm in all these brain regions, with maximal responses around mid-June, and minimal around mid-December (i.e., around solstices) (Fig. 2*B*).

Variations in PVT brain responses were not related to significant changes in PVT performance, which remained good and stable throughout the year ($P > 0.2$; Table S2). This guarantees that fMRI differences were not significantly biased by differences in performance to the task and suggests that fMRI is more sensitive than the behavioral tests we used in identifying seasonal variations in cognition. Stable performance throughout the year via distinct brain dynamics implies, however, that the "cost" of cognition (i.e., the neural resources involved in or at disposal for cognition) change with time of year. We hypothesize that the seasonality in brain responses could predict some of the seasonal variations in performance previously reported for potentially more sensitive tasks (11–13).

We next investigated whether other behavioral and physiological variables could account for the observed annual variations in PVT brain responses. Subjective and objective neurophysiological measures of alertness and subjective assessments of affective dimensions acquired immediately before fMRI acquisitions did not change significantly across seasons. In addition, in our dataset we could not replicate seasonal changes in melatonin secretion profile that were reported in some (30–33), but not all (34, 35), publications ($P > 0.05$; Table S2). Only self-reported mood varied significantly over season ($P = 0.003$; Table S2), but this variation was not significantly related to the seasonal changes in brain responses (Table 1 and Fig. S3). In summary, sustained attention-related brain activity fluctuates across seasons but these changes were not related to variations in the behavioral, endocrine, or neurophysiological parameters assessed in our study.

Photoperiod is the most obvious factor associated with season and both the intensity and spectral composition of light to which people are exposed vary with season (36). Fig. 2, indeed, suggests that PVT brain responses were closely related to photoperiod (gray area, Fig. 2*B*). A formal analysis revealed that all PVT brain responses showing seasonal variations were significantly associated with day length. This finding could imply that there is a "physiological memory" for the photoperiod to which participants were exposed before admission to the laboratory. Indeed, before fMRI recordings, participants had not seen sunlight for 4.5 d and had been for 63 h in dim light during wakefulness and in darkness during sleep episodes. Consistently, effects of prior light exposure ("photic memory") on cognitive brain responses have formerly been demonstrated on a much shorter timescale in humans (37) and photoperiod memory has previously been described as "after-effects" of photoperiod on circadian clock neurons in rodents (38). Whether our data reflect a true human photoperiod memory is, however, not possible to ascertain because many other environmental factors covary with season and photoperiod, including air temperature and humidity (Fig. 2*E*).

Having established seasonal/annual variations in sustained-attention-related brain responses, we then examined whether such variations could be generalized to other cognitive domains by considering the n-back task implemented in our protocol. We found that brain responses to this executive task varied significantly with season in the thalamus, including the pulvinar, and in prefrontal and frontopolar areas, similar to the PVT results. In addition, significant annual variation was observed in the insula, a brain region involved in executive processes, attention, and affective regulation (39) (Fig. 3*A* and Table 2). Compared with PVT brain responses, significant seasonal variations seemed to encompass a reduced set of brain areas, which could indicate a relative decrease in seasonality on executive brain responses, in line with previous suggestions of a reduced seasonal impact on behavioral measures of more complex tasks (13).

This qualitative task-specific difference was complemented by a statistically significant difference in the dynamics of brain response estimates across the year, with maximum and minimum responses being located ∼3 mo later for the n-back compared with the PVT (i.e., around autumn and spring equinoxes, respectively) (Fig. 3 *B* and *C*) (day of the year at responses maximum phase: PVT, 168.9 ± 8.2; n-back, 265.7 ± 13; $t_{11} = -20.16$; $P < 0.001$).

Similar to the PVT, performance on the n-back was good and stable throughout the year in our sample (Table S2). However, covariation with photoperiod was not significant for any of the executive brain responses that significantly varied with season. As depicted in Fig. 3, there seems, however, to be a striking similarity between annual dynamics in executive brain responses and day-to-day variation in daylength (i.e., the number of minutes of

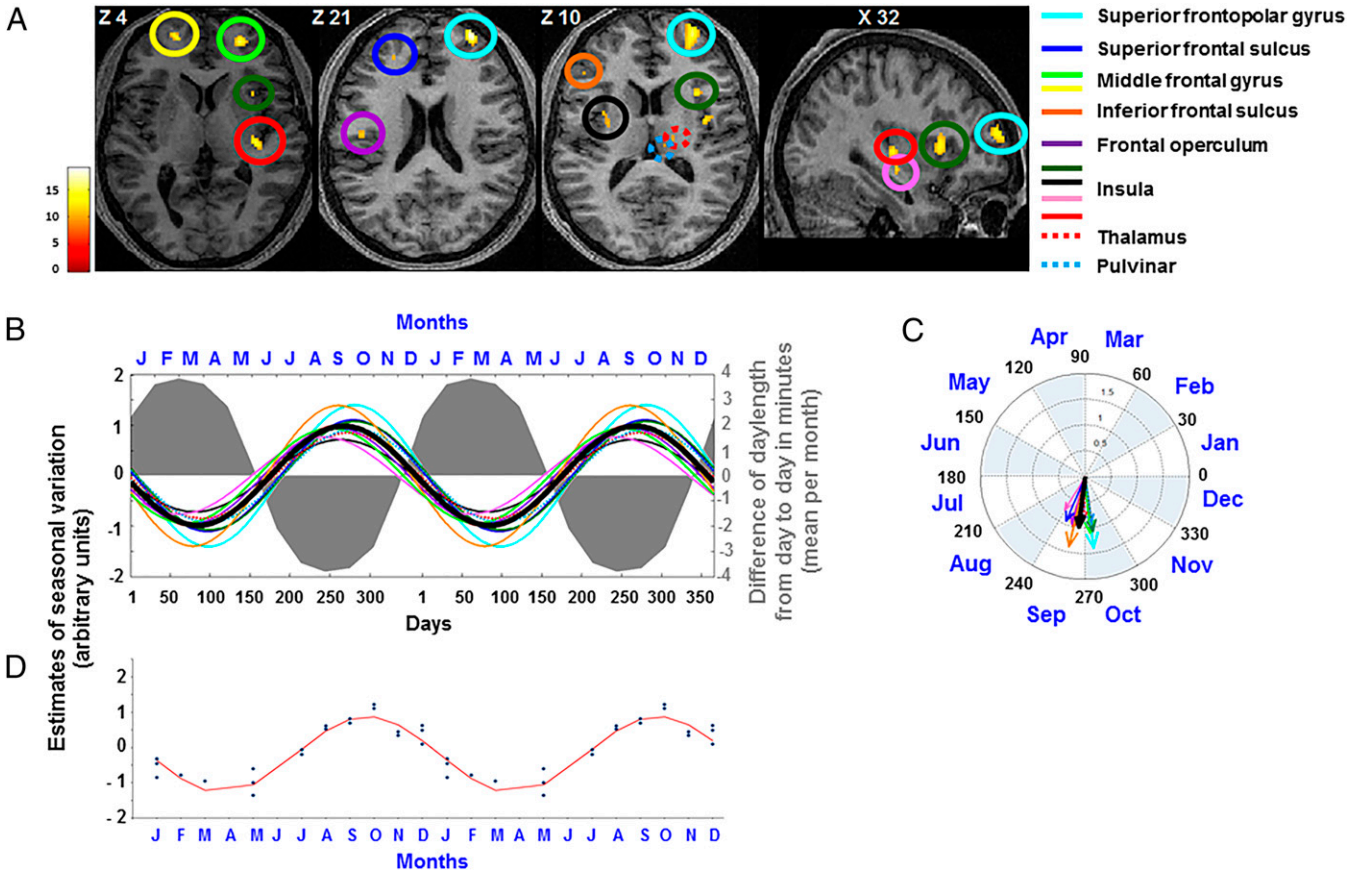

Fig. 3. Seasonal variations in executive brain activity. Display as in Fig. 2. (*A*) Significant ($p_{corrected} < 0.05$) seasonal variations in auditory three-back brain responses minus control task brain responses (simple letter detection). (*B*) Executive brain response estimates in regions of *A*. Gray area represents day-to-day change in photoperiod in Liège (minutes). (*C*) Same as *B* in polar coordinates. Maximum responses were located between 243° and 282° (mean 265.75) (i.e., September 3 and October 12) (mean September 22). (*D*) Double plot of individual activity estimates in a representative regions of *A* (middle frontal region) and its sinusoidal fit (red line).

day length gained or lost from one day to the next, which peaks at the equinoxes). This similarity is indeed confirmed statistically (Table 2). As for photoperiod, however, factors such as air temperature and humidity (Fig. 2*E*) covary with day-to-day day-length variations such that these are equally likely to contribute to seasonality in cognitive brain function.

Overall, the results provide clear evidence for seasonality in diverse types of cognitive processes and suggest that the annual dynamics are process-specific. One might postulate that more basic cognitive processes, such as attention, are more tightly related to basic environmental changes (e.g., day length), whereas higher cognitive processes are related to more complex cues, such as, for instance, social interactions (e.g., summer holidays usually encompass usually July and August in Belgium). This speculation cannot be tested here but would imply that brain response seasonal dynamics would be different in countries with different environmental and social constraints.

Interestingly, seasonal variations have been found in monoamines that are often related to cognitive functions, notably attention and executive processes (40, 41). Seasonal changes in serotonin levels in cerebrospinal fluid and blood as well as serotonin transporter binding have been repeatedly observed (but not systematically; see refs. 42 and 43), mostly leading to higher serotonin levels in summer (19, 44, 45) (i.e., with a pattern potentially similar to the annual variations we observed in PVT brain responses). As a matter of fact, sunlight-dependent variations in serotonin levels have been detected in cortical (frontal, cingulate, and insular cortex), limbic (amygdala and hippocampus), and subcortical (thalamus) areas (44–46), similar to those detected here in response to a PVT task. In contrast, the emerging seasonal pattern for dopamine brain concentration is characterized by higher levels in fall and lower levels in spring (47, 48), that is, with a pattern reminiscent of the annual variations in executive brain response observed in our sample. Similarly, seasonal variation in serum brain-derived neurotrophic factor concentration, a protein involved in learning and the regulation and plasticity of neuronal network, has been reported to undergo annual dynamics leading to higher circulating levels in the fall (49). Whether brain responses to learning tasks would have a similar annual pattern as the brain activity related to a working memory task remains to be investigated. As a whole, it seems that key modulators of brain function show at least some seasonality, potentially contributing to the seasonal changes in cognitive brain response we detected.

Influence of season is broad in the animal kingdom and encompasses locomotion, body mass, endocrine function (melatonin secretion), pelage, and sexual activity (1, 50, 51). Expression of at least part of the human genome seems to be seasonal (7), speaking for a potential broad impact of season also in humans. Our findings indicate that, in addition to time of day (2), time of year influences higher cognitive brain function in healthy participants. Our results have direct and important bearing on our understanding of intraindividual cognitive changes that could emerge at specific times of year.

Table 2. Seasonal variation in executive brain responses (three-back minus letter detection)

Brain areas	Side	X Y Z	Z score	*P* value
Superior frontopolar gyrus	R	32 56 18	4.16	0.001
Superior frontal sulcus	L	−24 42 22	3.19	0.032
Middle frontal gyrus	R	26 52 6	4.07	0.002
	L	−20 56 4	3.66	0.008
Inferior frontal sulcus	L	−50 30 14	3.20	0.031
Frontal operculum	L	−46 −14 20	3.29	0.024
Anterior insula	R	34 16 10	3.52	0.013
Insula	L	−30 −6 14	3.39	0.018
Posterior insula	R	38 −20 4	3.56	0.011
	R	34 −16 −6	3.34	0.021
Thalamus	R	16 −18 12	3.14	0.037
Pulvinar	R	10 −22 12	3.10	0.040

P values corrected for multiple comparisons over a priori small volume of interests. X Y Z: coordinates (millimeters) in Montreal Neurological Institute stereotactic space. No regions survived inclusive masking ($p_{uncorrected} < 0.001$), whereas all regions survived exclusive masking ($p_{uncorrected} < 0.05$) with a brain map of the potential executive brain responses covarying with (*i*) daylength, (*ii*) subjective mood, and (*iii*) three-back performance (d-prime), suggesting that annual variations in all regions are not significantly driven by these variables. Most regions survived inclusive masking ($p_{uncorrected} = 0.001$) consisting of a brain map of the potential executive brain responses covarying with day-to-day day-length variation, suggesting that annual variations in all regions, except thalamus and pulvinar, are significantly driven by the seasonal changes in day-to-day day-length variation. L, left; R, right.

Materials and Methods

Additional methodological descriptions are provided in *SI Materials and Methods*.

The study was approved by the local Ethics Committee of the University of Liège and participants gave their written informed consent. Participants underwent first 3 wk of a controlled sleep–wake schedule before the in-laboratory procedure which began in the evening of day 1 and ran over four nights (Fig. S1). This period was completed in the absence of seasonal cues (no access to daylight or external information such as internet access or cellular phones). Starting on the morning of day 3, participants remained awake for 42 h under constant routine (CR) conditions during which endocrine, neurophysiology, and neuropsychological measures were regularly collected. Sleep deprivation was followed by a 12-h recovery night in darkness. Day 5, while the participant were still in dim light, was devoted to an fMRI session that was carried out 1 h after wake up and is the main focus of the current paper. Subjective sleepiness and affective dimensions were assessed hourly throughout the protocol.

Cognitive Tasks. The fMRI session included two cognitive tasks separated in two acquisition runs. The PVT required pressing a button as quickly as possible when a stopwatch pseudorandomly started in the center of the screen. Mean interstimulus interval was set to be between 2 and 10 s and trial duration was a maximum of 10 s. The auditory three-back implies to state whether or not a consonant was identical to the consonant presented three stimuli earlier. Stimulus onset interval was set at 2 s. Letters were presented in block of 30 consonants separated by 10 to 20 s of rest. Six blocks of three-back were presented to each participant in addition to four blocks of a letter detection task consisting of identifying the letter "k" in a stream of consonants (same block duration and stimulus interval).

fMRI Data Analysis. Data were spatially preprocessed (standard parameters) and analyzed using SPM8 (www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.10 (MathWorks Inc.). Statistical analysis proceeded in two steps, a fixed and a random effects analysis, to take into account the variance at the individual and at the group level, respectively. Each trial type of the PVT and each hit of the three-back and letter detection task were modeled using stick functions, convolved with a canonical hemodynamic response function. For the PVT 20% fastest, 20% slowest, and intermediate reaction times and lapses were modeled as separate regressors. For the n-back, three-back, and letter detection task trial types were modeled separately. The design matrix also included regressors for movement parameters, derived from realignment of functional volumes, which were considered as covariates of no interest. A high-pass filter was implemented using a cutoff period of 128 s. Contrasts of interest consisted of the main effect of the intermediate reaction times of the PVT and the executive component of the three-back (three-back hits minus letter detection hits). These individual contrast images were entered in the second-level analysis. This latter random effects analysis included two covariates consisting of year-long period sine and cosine functions for which each day of the year (day 1 = January first) is almost equivalent to 1° (365 d for 360°).

Statistical inferences were performed using *F* test combining both sine and cosine covariates and thresholded at $P < 0.05$ after corrections for multiple comparisons (familywise error method) over the entire brain volume or over small spherical volumes (10-mm radius) around a priori locations of interest taken from literature (*SI Materials and Methods*).

Significant *F* tests indicate voxels with a response showing a seasonal variation with annual periodicity. From the parameters of the sine and cosine regressors, the phase and amplitude of the seasonal effect are estimated as the arctangent of the ratio of the parameters and the square root of their sum of square, respectively:

$$\begin{aligned} R(t) &= betas*\sin(2*\pi*t/T) + betac*\cos(2*\pi*t/T) + \varepsilon \\ &= A*\cos(2*\pi*t/T - \varphi) + \varepsilon \end{aligned}$$

and

$$\varphi = \text{atan2}(betas, betac)$$

$$A = \text{sqrt}(betas^2 + betac^2),$$

where R is the voxel response, betas/betac are the parameters for the sine/cosine regressors, T is the period of 1 y, ε is the residual of the model, φ is the phase of the seasonal response [R is maximum at $tMAX = \varphi*T/(2*\pi)$], and A is the amplitude of the seasonal response.

Four additional separate random effects analyses included (*i*) day length, (*ii*) subjective mood, (*iii*) day-to-day day-length variation, and (*iv*) behavioral performance (PVT performance: median, 20% fastest, and 20% slowest reaction times; three-back performance: d-prime) as covariates to constitute maps of the brain areas covarying with each variable. Maps were used as inclusive or exclusive masks over the results of the seasonality analyses thresholded at $P < 0.001$ or $P < 0.05$ uncorrected, respectively.

Behavioral and Physiological Data Analysis. Multiple regression analyses searching for seasonal variation in behavioral measures were performed (STATISTICA 10; StatSoft) using sine and cosine as independent variables. We tested their influence on (*i*) the subjective sleepiness alone, (*ii*) the six affective dimensions of the visual analog scale, (*iii*) PVT median reaction time, lapses, per 20 and per 80 together, and (*iv*) and three-back d-prime and criterion together.

Similar multiple regression analyses searching for seasonal variation in physiological and endocrine measures were also performed. Dependent variables were grouped as follows: (*i*) theta and alpha power on Cz together; (*ii*) melatonin amplitude, DMOn, DLMOff, midpoint, and width; (*iii*) total sleep time, sleep efficiency, stage-two and slow wave, each one separately, for baseline night and recovery night; and (*iv*) the timing of the last fMRI session relatively to DLMon and DLMoff.

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