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Seasonality in regional brain glucose metabolism

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Original Article

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Abstract

Background. Daylength and the rates of changes in daylength have been associated with seasonal fluctuations in psychiatric symptoms and in cognition and mood in healthy adults. However, variations in human brain glucose metabolism in concordance with seasonal changes remain under explored.

Methods. In this cross-sectional study, we examined seasonal effects on brain glucose metabolism, which we measured using 18F-fluorodeoxyglucose-PET in 97 healthy participants. To maximize the sensitivity of regional effects, we computed relative metabolic measures by normalizing the regional measures to white matter metabolism. Additionally, we explored the role of rest–activity rhythms/sleep–wake activity measured with actigraphy in the seasonal variations of regional brain metabolic activity.

Results. We found that seasonal variations of cerebral glucose metabolism differed across brain regions. Glucose metabolism in prefrontal regions increased with longer daylength and with greater day-to-day increases in daylength. The cuneus and olfactory bulb had the maximum and minimum metabolic values around the summer and winter solstice respectively (positively associated with daylength), whereas the temporal lobe, brainstem, and postcentral cortex showed maximum and minimum metabolic values around the spring and autumn equinoxes, respectively (positively associated with faster daylength gain). Longer daylength was associated with greater amplitude and robustness of diurnal activity rhythms suggesting circadian involvement.

Conclusions. The current findings advance our knowledge of seasonal patterns in a key indicator of brain function relevant for mood and cognition. These data could inform treatment interventions for psychiatric symptoms that peak at specific times of the year.

Introduction

Like many species, humans adapt to environmental changes such as light–dark cycles across seasons. Seasonal adaptations have been reported for numerous biological pathways including gene transcription, neurotransmitter, neuropeptides, immune, metabolic, and neuroendocrine process (Dopico et al., 2015; LaDage, 2022; Wehr, 1998). A recent transcriptome study showed that the brain exhibited the highest seasonality across different tissue types (Wucher, Sodaei, Amador, Irimia, & Guigó, 2023). Increasing evidence suggests seasonal variations in brain functions (Zhang, Shokri-Kojori, & Volkow, 2023; Zhang & Volkow, 2023). Across countries, there is an association between mood and daylength, and positive affect in social media posts increases when days become longer (Golder & Macy, 2011). Interestingly, although less studied than mood, cognitive brain responses also display seasonal patterns (Meyer et al., 2016; Polich & Geisler, 1991), which appear to be process-specific (Meyer et al., 2016).

Humans are very sensitive to light, which is considered as a key contributor to seasonal effects. Acute light exposure improved alertness, enhanced cortical activation during a non-visual attention task, and modulated emotional processing (Perrin et al., 2004; Vandewalle et al., 2010; Vandewalle, Maquet, & Dijk, 2009). These non-visual effects of light are largely mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs) that project to regions involved in cognition and emotion, but also to the suprachiasmatic nucleus (SCN), which is the main brain circadian pacemaker (Fernandez et al., 2018; Hattar, Liao, Takao, Berson, & Yau, 2002; LeGates et al., 2012). The SCN encodes information of daylength and plays an important role in seasonal control. Human postmortem studies revealed that the volume and number of vasopressin neurons in the SCN vary across the year in association with daylength and the rates of daylength changes (Hofman, Purba, & Swaab, 1993; Hofman & Swaab, 1993). Therefore, light changes across seasons might affect the brain through circadian pathways (Zhang & Volkow, 2023).

Glucose serves as the brain's main energy source and measures of regional brain glucose metabolism are used as markers of regional brain function (Dienel, 2019). Task-induced changes in glucose metabolism spatially overlap with brain activations and increase with

higher cognitive demand (Ripp et al., 2021), whereas hypometabolism is associated with cognitive decline (Yang, Cummings, Kinney, Cordes, & Alzheimer's Disease Neuroimaging Initiative, 2023). There is evidence that regional brain glucose metabolism is sensitive to light. Specifically, five days of bright light exposure increased metabolism in the olfactory bulb and hippocampus, which are regions closely tied to neurogenesis (Kohno et al., 2016). So far, seasonal effects on brain glucose metabolism remain under investigation. Here we examined seasonality in cerebral glucose metabolism using 18F-fluorodeoxyglucose (FDG)-PET. Since daylength and day-to-day changes in daylength have distinct effects on mood and various cognitive processes (Meyer et al., 2016), we expected that their effects would differ between brain regions. In this study, we assessed rest–activity rhythm (RAR), which is strongly modulated by the internal clock and often used as a proxy measure of endogenous circadian rhythm. We tested seasonal variations in RAR as well as its relationship with cerebral glucose metabolism.

Methods

Participants

Participants were recruited through referrals from the NIH Volunteer Office, the Patient Recruitment and Public Liaison office, and ResearchMatch.org. Participants who in the past two weeks used psychoactive medications or medications that can affect brain function such as tricyclic antidepressants and selective serotonin reuptake inhibitors, who had a current or past DSM diagnosis of a psychiatric disorder including substance use disorder (except for nicotine), who had a binge history in the last 10 years, who had major medical problems at the time of the scan were excluded.

Data from 97 healthy participants (age: 41.64 ± 13.82; 46 female) were collected between February 2015 and December 2018. The daylength varied between 10.43 and 15.98 h. The changes of daylength compared to the previous day ranged from −2.57 to 2.62 min. Negative values indicate daylength loss whereas positive values indicate daylength gain. The minima and maxima for daylength correspond to the winter and summer solstice respectively, while the period of greatest daylength change corresponds to the Spring (greatest daylength gain) and to the Autumn equinox (greatest daylength loss) (Fig. 1).

All participants were asked to arrive at the National Institutes of Health at 09:00 am on the PET scan day and were scanned between 11:00 am and 01:00 pm. Participants were not allowed to eat any food or consume any nicotine or caffeine after arriving at NIH (i.e. at least 2 h before the scan). A total of 89 participants had one-week actigraphy data. We excluded participants ($n = 5$) who had less than four valid days that is a minimum of 16 h wearing time per day. Among the 84 participants, 76 had actigraphy data collection close to when their FDG-PET scan was done (differences in daylength less than 1 h). Therefore, only the data from 76 participants were used to test the association between RAR and cerebral glucose metabolism. The averaged days between FDG-PET scan and actigraphy assessment were 1.80 ± 7.09 days. Written informed consent approved by the Institutional Review Board at the NIH was obtained from all participants.

FDG-PET scanning and MRI data acquisition

FDG-PET scan was performed using a high-resolution research tomography (Siemens AG, Germany) with ∼2.5 mm camera resolution. Prior to the PET imaging session, participants were instructed to fast for at least 4 h (except for water). Two venous catheters were inserted, one for measuring the concentration of radioactivity from arterialized venous blood, and the other for radiotracer injection. A transmission scan using cesium-137 was obtained before tracer injection to correct for attenuation. Intravenous injection of FDG (8 mCi) was then administered over approximately 1 min. PET emission scans were obtained in list mode (one image every 10 s), starting immediately after FDG injection, and continuing for 75 min. A Polaris Vicra head tracking system (Northern Digital Inc., ON, Canada) was used to track head movement during the PET scan, and this information was used in the image reconstruction process to minimize motion-related image blurring. Direct reconstruction of dynamic brain PET with event-by-event motion correction was implemented (Germino, Gallezot, Yan, & Carson, 2017). During the PET imaging procedure, participants rested quietly under dim illumination and minimal acoustic noise. A summary image was obtained between 35 and 75 min (voxel size: 1.23 mm isotropic, 207 slices). To ensure that participants remained awake, they were monitored throughout the procedure and asked to keep their eyes open.

Anatomical brain images were acquired using a 3.0 T Magnetom Prisma scanner (Siemens Medical Solutions USA, Inc., Malvern, PA, USA) with a 32-channel head coil. A total of 32 participants were scanned under the protocol using T1-weighted 3D MPRAGE (TR/TE = 2200/4.25 ms, FA = 9 deg, 1 mm isotropic) and T2-weighted spin-echo multi-slice (TR/TE = 8000/72 ms, 1.1 mm in-plane resolution, 1.7 mm slice thickness, 94 slices) pulse sequences to acquire high-resolution anatomical brain images. A total of 65 participants were scanned under the protocol using T1-weighted 3D MP-RAGE (TR/TE = 2400/2.24 ms, FA = 8 deg, 0.8 mm isotropic) and variable flip angle turbo spin-echo (Siemens SPACE; TR/TE = 3200/564 ms) pulse sequences to acquire high-resolution anatomical brain images. The scan days for the two protocols significantly differed in rates of daylength changes ($t = 3.90$, $p < 0.001$) but not in daylength ($t = 1.12$, $p = .264$). MRI data were processed using the minimal preprocessing pipeline of the Human Connectome Project (Glasser et al., 2013). FreeSurfer v5.3 was used for anatomical segmentation and to obtain brain masks, i.e. white matter mask (Desikan et al., 2006).

FDG-PET analyses

The voxel-level measurement of cerebral metabolic rate of glucose consumption (CMRglc) was calculated using PMOD v3.4 (PMOD Technologies, Zurich, Switzerland) based on an autoradiographic solution for the two-tissue compartment model, up to the mid-time of the summary image (55 min) (Huang et al., 1980; Phelps et al., 1979). Gray matter parameters were $k_1 = 0.102\ \text{min}^{-1}$, $k_2 = 0.130\ \text{min}^{-1}$, $k_3 = 0.062\ \text{min}^{-1}$, $k_4 = 0.0068\ \text{min}^{-1}$, and $LC = 0.52$. The resulting CMRglc maps were aligned to the individual subject's anatomical space and then normalized to MNI space using FSL parameters. No smoothing was applied. To minimize inter-subject variability in brain metabolism and maximize sensitivity to regional effects, the CMRglc maps were normalized to relative metabolism measures (rCMRglc) using FSL command line utilities (Ishibashi, Wagatsuma, Ishiwata, & Ishii, 2016; Wang, Volkow, Wolf, Brodie, & Hitzemann, 1994). Regional measures were normalized to metabolism in whole white matter, which was used as a reference region because its metabolism is not affected by neural activity or neurotransmitters

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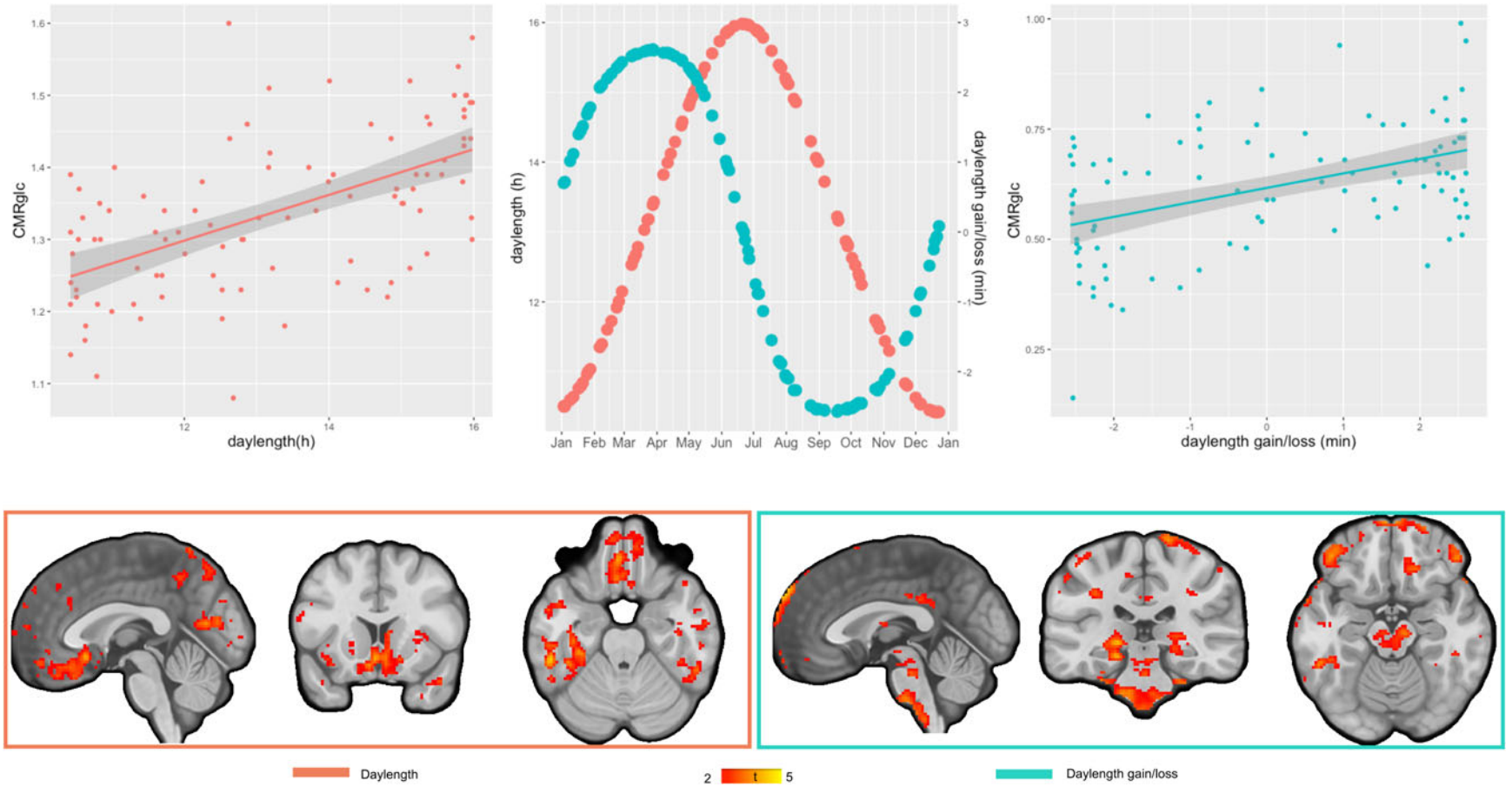

Figure 1. Seasonal effects on rCMRglc. Middle: Daylength (red) and day-to-day changes in daylength (blue) when the FDG-PET scan were obtained for the 97 participants. Left: Effects of daylength on rCMRglc. (Upper) Linear plot of daylength with rCMRglc values extracted from significant clusters. (Bottom) t-map of the association of rGMRglc with daylength. Right: Effects of day-to-day changes in daylength on rCMRglc. (Upper) Linear plot of day-to-day changes in daylength with rCMRglc values extracted from significant clusters. (Bottom) t-map of the association of rCMRglc with day-to-day changes in daylength.

that vary across seasons (Zhang & Volkow, 2023). The lack of seasonal variations in white matter metabolism was confirmed by examining associations of absolute white matter CMRglc with daylength and rates of daylength changes (see Results).

We used statistical Parametric Mapping version 12 (SPM12; Wellcome Trust Center for Neuroscience, London, UK) implemented in MATLAB version R2017a (MathWorks, Natick, MA, USA) for second-level analyses. A multiple regression model was applied. Daylength and day-to-day changes in daylength were included as two variables of interest; age and gender were included as covariates. Significance thresholds were set at voxel-level uncorrected $p < 0.005$ and cluster-level FWE-corrected $p < 0.05$, cluster size $k > 100$.

Actigraphy analysis

To record rest–activity patterns/sleep–wake activity, participants wore a GENEActiv triaxial accelerometer (Version 1.1; Activinsights Ltd., Cambridgeshire, UK) placed on the non-dominant wrist continuously for one week. For actigraphy analyses, we applied both parametric and non-parametric measures as they are complimentary. While parametric measures capture the size, timing, and shape of rhythms (Marler, Gehrman, Martin, & Ancoli-Israel, 2006), non-parametric measures are based on raw data counts and do not rely on *a priori* assumptions about the waveform, e.g. a cosine shape of activity data (van Someren et al., 1996). For parametric analysis, acceleration data were averaged within 60 s epochs using GENEActiv PC Software 3.0. A sigmoidally transformed extended cosine model adapted from Marler et al. (2006) was applied to fit the rest–activity data using R package RAR (v2.0.0). For non-parametric analysis, we used the R package GGIR (v2.4-0) to process the raw accelerometer data in .bin format (van Hees et al., 2014, 2015). Seventeen RAR variables were calculated. *Parametric measures*: *alpha* (greater values means narrower active period), *acrophase* (time of peak activity level), *amplitude* (peak-nadir difference), *up-mesor* (time when activity passes up through mesor, approximately the time of increasing activity in the morning), *down-mesor* (time when activity passes down through mesor, approximately the time of settling down for the night), *pseudo-F statistic* (how well the obtained rest–activity data fitted the 24 h rhythm model; lower *F* values indicate poorer model fit and greater rhythm irregularity). *Non-parametric measures*: *M10* (the 10 h period of maximum activity, roughly daytime activity level), *daily mean activity* (the activity across 24 h), *sleep onset*, *wakeup time*, *sleep duration* and *their day-to-day variations*, *M10hr* (M10 starting time); *intra-daily variability* (IV; the variations of rest–activity rhythm within each 24 h period), *inter-daily stability* (IS; the similarity of one 24 h period to the next). SPSS 22 (IBM, Armonk, NY, USA) was used for factor analyses to extract RAR principal components with varimax rotation.

Statistics

Daylength and its day-to-day variations were calculated as the daytime plus civil twilight on the study days using R package 'suncalc', where calculations were based on geographic location of the study locations: Bethesda, Maryland, USA: latitude = 39.00, longitude = −77.10. Gain/losses of daylength were calculated by subtracting the daylength of the day prior to study days (PET scan day or the first day of actigraphy) from the daylength of the study days.

We examined the associations of daylength and day-to-day changes in daylength with RAR principal components. Same as for the brain analyses, a multiple regression model was applied for each RAR component. Daylength and the rates of daylength changes were included in the model as variables of interest, while age and gender were included as covariates. Also, we tested associations between rCMRglc and RAR components that showed significant seasonal variations using Pearson's correlations. SPSS 22 (IBM, Armonk, NY, USA) was used.

Results

Cerebral glucose metabolism associated with daylength and day-to-day changes in daylength

The multiple regression model showed that daylength and the day-to-day changes in daylength had independent effects on rCMRglc. While longer daylength and greater increases in daylength both contributed to increased rCMRglc in the frontal lobe, they also had distinct effects: rCMRglc in the Cuneus and Olfactory bulb strongly correlated with daylength, whereas rCMRglc in the brainstem, postcentral, and temporal pole was associated with the rates of daylength increases (Table 1). rCMRglc associations with the rates of daylength increases also survived a more stringent threshold of voxel-wise uncorrected $p < 0.001$ and cluster-level FWE-corrected $p < 0.05$ (Table S1).

Table 1. The independent effects of daylength and day-to-day changes in daylength on CMRglc

Regions	*t*	*z*	*k*	Peak coordinates (*x*,*y*,*z*)		
Daylength						
Mid frontal	4.78	4.51	434	−29	60	15
Cuneus_L	4.02	3.85	201	−7	−78	17
Olfactory	3.84	3.69	286	−3	16	−11
Cuneus_R	3.54	3.42	238	9	−88	33
Daylength gain/loss						
Frontal_Sup_Medial	5.17	4.83	968	21	58	27
Temporal pole	4.42	4.20	253	27	12	−45
Brainstem	4.06	3.89	394	−15	−42	−61
Postcentral	3.82	3.67	198	17	−40	79

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CMRglc in the white matter was not associated with daylength (b = 0.23, p = 0.517) or rates of changes in daylength (b = 0.47, p = 0.181).

RAR associated with daylength and day-to-day changes in daylength

We extracted four RAR components from 17 RAR variables that explained 71.4% of the total variance (Table 2). Please see Table 3 for descriptive results for the 17 RAR variables. We identified four RAR components and labeled them with the greatest loadings of each component: (1) late phase timing; (2) narrow active period; (3) high physical activity and inter-daily stability; (4) sleep irregularity and short sleep duration. Longer daylength was associated with higher physical activity and inter-daily stability (component 3) (b = 0.12, p = .037). No other associations were significant (Fig. 2).

Brain–RAR associations

Since RAR component 3 physical activity and inter-daily stability showed significant seasonal fluctuations, we examined its association with rCMRglc in the regions that were influenced by daylength. Higher physical activity and stability were associated with greater rCMRglc in the olfactory bulb (r = 0.27, p = 0.020; Fig. 3).

Discussion

The current study provides evidence that daylength and day-to-day changes in daylength independently contribute to seasonality in cerebral glucose metabolism. Additionally, RAR, a proxy measure for the endogenous circadian rhythm showed annual variations (Ancoli-Israel et al., 2003). Higher physical activity and inter-daily stability were associated with daylength and daylength-related cerebral glucose metabolism but not rates of daylength changes.

Changes in photoperiod are believed to serve as a primary driver for seasonal adaptations (Forni et al., 2014). Specifically, it has been proposed that humans may have a 'photic memory' for the photoperiod. A cross-sectional study in healthy young participants (n = 28) who were tested after living without any seasonal cues for 4.5 days throughout the year observed that attentional processes were influenced by daylength, while executive brain responses were associated with day-to-day changes in daylength (Meyer et al., 2016). In line with this, our findings also support independent contributions of daylength and rates of daylength changes to seasonal effects on cerebral glucose metabolism. Consistent also with Meyer's report on cognitive brain responses (Meyer et al., 2016), we found that rCMRglc in the superior medial and middle frontal gyrus – regions that play important roles in various cognitive processes (Amodio & Frith, 2006; du Boisgueheneuc et al., 2006; Hu, Ide, Zhang, & Li, 2016) and in emotional regulation (Wang et al., 2021; Waugh, Lemus, & Gotlib, 2014) – were sensitive to both daylength and rates of daylength changes. Moreover, the regions associated with daylength or day-to-day changes in daylength have previously been shown to be affected by acute light exposure. Specifically, acute light exposure increased alertness and cognitive brain responses including activations in the middle frontal gyrus, brain stem, temporal,

Table 2. Four RAR principal components extracted from 17 RAR variables

Rotated component matrix				
	Comp 1	Comp 2	Comp 3	Comp 4
alpha		0.971		
acrophase	0.938			
Amplitude_log				
Up-mesor		0.855		
Down-mesor	0.519	−0.816		
F_stat			0.633	
M10			0.917	
M10hr	0.827			
Daily physical activity			0.922	
IS_interdailystability			0.661	
IV_intradailyvariability				
Sleep duration				−0.538
Sleep duration_variation				0.606
sleeponset	0.896			
sleeponset_variation				0.823
Wakeup time	0.804			
Wakeup time_variation				0.843

Extraction method: principal component analysis.
Rotation method: varimax with Kaiser normalization.
Coefficient values >0.5 are listed.

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Table 3. Descriptive information for 17 RAR variables

17 RAR variables	Mean (s.d.)
alpha	−0.47 (0.40)
Acrophase (24 h decimal time)	15.55 (1.39)
Amplitude_log	1.79 (1.66)
Up-mesor (24 h decimal time)	7.34 (2.50)
Down-mesor (24 h decimal time)	13.75 (3.00)
F_stat	772.38 (396.05)
M10 (mg)	47.92 (24.34)
M10hr (24 h decimal time)	10.35 (1.65)
Daily physical activity (mg)	28.76 (11.87)
IS_interdailystability	0.50 (0.13)
IV_intradailyvariability	0.73 (0.18)
Sleep duration (h)	7.09 (1.33)
Sleep duration_variation (h)	1.68 (0.77)
Sleeponset (24 h decimal time)	24.10 (1.65)
sleeponset_variation (h)	1.62 (1.03)
Wakeup time (24 h decimal time)	31.19 (1.81)
Wakeup time_variation (h)	1.59 (1.14)

and parietal regions (Vandewalle et al., 2006, 2007a, 2007b). Five-day bright light exposure increased glucose metabolism in the olfactory bulb (Kohno et al., 2016). In our study, daylength was associated with higher rCMRglc in the olfactory bulb, which plays an important role in emotion processing and memory (Mouly & Sullivan, 2010; Soudry, Lemogne, Malinvaud, Consoli, & Bonfils, 2011) and in the cuneus, which is involved in visual perception (Vanni, Tanskanen, Seppä, Uutela, & Hari, 2001) but has also been implicated in the modulation of emotional states including symptoms of depression (Dotson, Bogoian, Gradone, Taiwo, & Minto, 2022; Foland-Ross, Cooney, Joormann, Henry, & Gotlib, 2014). In contrast, rapid increases in daylength were associated with increased metabolism in the temporal pole, brainstem, and postcentral cortex. The temporal pole is believed to integrate complex perceptual inputs to emotional responses (Olson, Plotzker, & Ezzyat, 2007) and is relevant for sematic memory (Chadwick et al., 2016). The brainstem receives and integrates signals from the body communicating them to cortical and subcortical brain regions. Isolated lesions in the brainstem lead to various cognitive and affective impairments in patients (Fu et al., 2017). The precentral gyrus as a part of primary motor cortex is responsible for voluntary motor movement and sensorimotor integration (Andersen & Buneo, 2003). Thus, daylength and rate of daylength changes could affect activity in different brain regions and distinctly impact cognition, emotions, and behavior. Seasonal adaptations in neurotransmitters, particularly serotonin and dopamine, may underlie observed seasonal changes in cerebral glucose metabolism (Zhang & Volkow, 2023). So far, most studies on seasonality have been based on the calendar for seasonal classification; future studies, which consider daylength variations and involve more time measurements, are needed to understand seasonal adaptations in neurobiological mechanisms at multiple levels. The obtained knowledge will help us understand better the different seasonal patterns of psychiatric symptom presentations. While brain adaptations associated with daylength might account for symptoms that peak at the Winter/Summer solstice, brain adaptations associated with rates of daylength changes might explain symptoms that peak at the Autumn/Spring equinoxes when the daylength changes are the fastest (Zhang & Volkow, 2023).

Since the effects of acute light exposure are relatively short, the observed photoperiod memory could reflect 'after effects' of the photoperiod on the internal clock (Chellappa et al., 2014; Meijer, Michel, Vanderleest, & Rohling, 2010). The SCN transmits daylength information by exhibiting daily variations in the volume and number of vasopressin neurons with two peaks around twilight (Hofman & Swaab, 1993). Moreover, the highest volume and number of vasopressin neurons occur in October when daylength becomes shorter and the rates of decreases are the greatest and there is another smaller peak around March when the rate of increase in daylength accelerates (Hofman et al., 1993). Conversely, the lowest volume and number of neurons are observed around June when the day length is longest and day-to-day changes in daylength are minimal (Hofman & Swaab, 1993; Hofman et al., 1993). According to the extensive projections of SCN to various subcortical and cortical regions, the seasonal adaptions in the SCN can have extensive downstream effects on brain functions (Hastings, Maywood, & Brancaccio, 2018). These findings suggest that SCN adaptations may optimize brain response to dramatic photic transitions during twilight and equinox, which are critical for the regulation of daily and annual activities. As RAR is strongly modulated by the internal clock, we used it as a proxy measure for the endogenous circadian rhythm (Ancoli-Israel et al., 2003). We found that longer daylength and daylength-associated increases in rCMRglc in the olfactory bulb were associated with higher physical activity and greater rhythm regularity, which are consistent with the effect of light on RAR (Esaki et al., 2023; Skeldon, Dijk, Meyer, & Wulff, 2022). Light is the most important regulator of endogenous circadian rhythms, as greater daytime light exposure increased levels of physical activity and the stability of RAR (Esaki et al., 2023; Skeldon et al., 2022). In addition to RAR, direct associations between daytime light exposure and enhanced amplitude and robustness of endogenous circadian rhythms have been reported in diurnal animals (Bano-Otalora et al., 2021). Our findings indicate a strong circadian involvement associated with daylength but not with the rates of daylength changes.

Some limitations of the current study may restrict our conclusions. First, this is a cross-sectional study and longitudinal data with high-temporal resolutions are required to better understand the within-subject changes across the seasons. Second, apart from light changes in the environment, social and cultural factors could have a significant impact on an individual's light exposure. Since light exposure during daytime and nighttime can have opposite effects on circadian rhythm (Esaki et al., 2023), not only the amount but also the timing of light exposure could lead to individual differences in seasonal effects. In this study, PET scans were performed under a dim light condition. However, we did not control for light exposure prior to the PET scan, which could vary across seasons. Thus, we cannot differentiate the influence of acute light exposure from that of photoperiod. As our findings with RAR suggest a circadian involvement, i.e. higher physical activity and inter-daily stability were associated with longer daylength and related rCMRglc, it is less likely that the observed variations in brain glucose metabolism are fully explained by acute light exposure. The current findings may be

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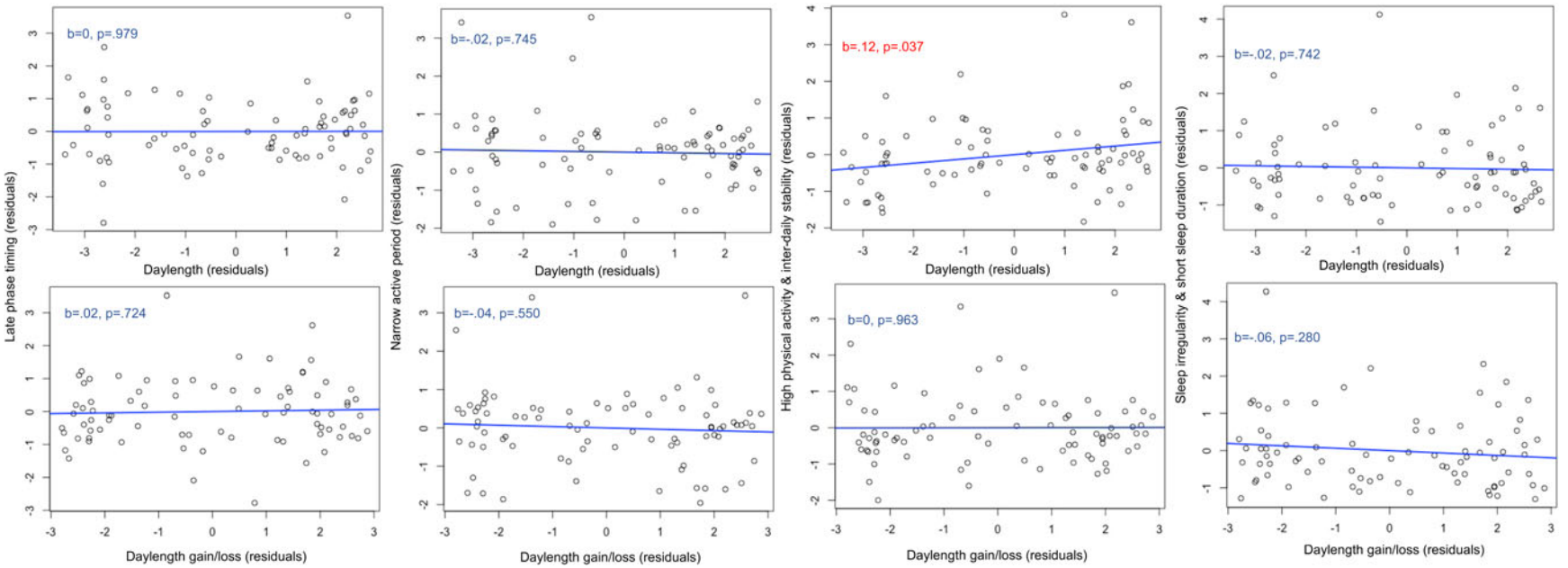

Figure 2. Seasonal variations in RAR. Partial regression plots for associations of four RAR components (*y*-axis) with daylength or daylength gain/loss (*x*-axis) in 84 participants.

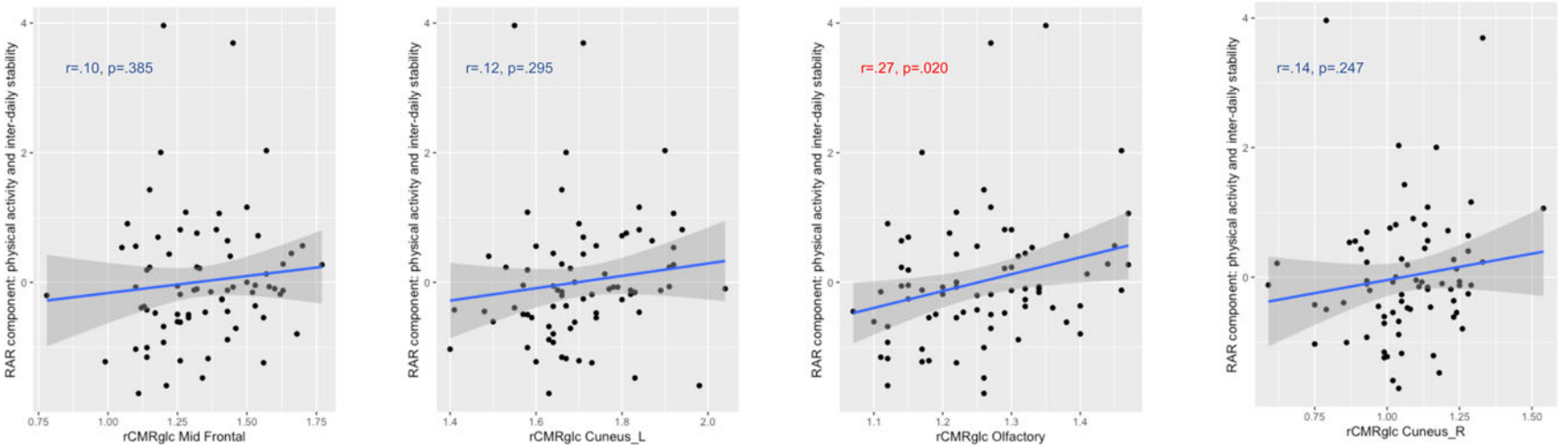

Figure 3. Physical activity and daylength-associated rCMRglc. Associations of RAR component high physical activity and inter-daily stability with daylength-related rCMRglc in midfrontal gyrus, cuneus, and in olfactory bulb in 76 participants.

affected by both photoperiod-induced circadian changes and by acute light exposure, which reflect seasonal variations in brain glucose metabolism in a real-life scenario. Another limitation for the study was that we did not obtain sleep diaries for the participants and that the actigraphy data were obtained close to the day of scanning (1.80 ± 7.09 days) but not up to the scanning, which would have given us a more precise delineation of activity close to the time of measurements. Also, because our study evaluated seasonal variations in brain glucose metabolism in real life, and not in a laboratory or experimentally controlled set-up, which would have allowed us to control the sleep–wake cycles (e.g. by imposing sleep–wake schedule). In future studies of seasonal effects, measures of light exposures and the use of sleep diaries would allow to investigate more precisely the effects of sleep behaviors, light exposures and seasonal effects. Also, direct measures of the endogenous circadian rhythm such as melatonin onset are required to corroborate whether the long-lasting effect of photoperiod is exerted through circadian pathways. Finally, participants were scanned under two protocols that differed in the MRI acquisitions. Since the structural images were used for the preprocessing of the PET images including alignment, normalization, and segmentation, this could have impacted our findings. As the two protocols significantly differed in rates of daylength changes, controlling for different protocols could diminish the effect that we are interested in, i.e. effect of rates of daylength changes. Future studies are needed to replicate our findings.

In conclusion, the current finding provides evidence for independent associations of daylength and rates of day-to-day changes in daylength with cerebral glucose metabolism. A better understanding of neurobiological pathways associated with daylength and daylength changes would advance our knowledge of seasonal patterns in mood and cognition including in the presentation of psychiatric symptomatology and could help guide treatment interventions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000436.

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