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Sunshine-exposure variation of human striatal dopamine D_2/D_3 receptor availability in healthy volunteers

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ABSTRACT

Background: In addition to the serotonergic system, the central dopaminergic system has been reported to be correlated with seasonality. The aim of this study was to explore the difference in striatal dopamine D_2/D_3 receptor availability between healthy volunteers who had a high-sunshine exposure and those who had a low exposure.

Methods: Sixty-eight participants were enrolled, and those in the upper and lower quartiles in terms of sunshine exposure were categorized into high- ($n=17$) and low-sunshine-exposure ($n=18$) subgroups. Single photon emission computed tomography with [^{123}I] iodo-benzamide was used to measure striatal dopamine D_2/D_3 receptor availability.

Results: Striatal dopamine D_2/D_3 receptor availability was significantly greater in the subjects with high-sunshine exposure than in those with low-sunshine exposure ($F=7.97$, $p=0.01$) after controlling for age, sex, and smoking status.

Limitations: Different subjects were examined at different time points in our study. In addition, the sex and tobacco use distributions differed between groups.

Conclusion: The central dopaminergic system may play a role in the neurobiological characteristics of sunshine-exposure variation.

1. Introduction

Epidemiological studies have shown that mood alterations in response to seasonal changes, usually in winter, may be represented by a single dimension known as "seasonality" (Kasper et al., 1989). Thus, seasonal affective disorder (SAD) may represent an extreme, pathological variation of a dimensional population trait (Spoont et al., 1991). Many factors potentially vary with season, such as humidity, sunshine exposure, and temperature; nevertheless, sunshine exposure has been a central research focus and is thought to possibly result in the alteration of monoamine neurotransmitter activity between seasons (Oren, 1991). Many studies have focused on disturbance in serotonin levels (Koskela et al., 2008; Praschak-Rieder et al., 2008), but others have found that alterations in central dopamine functional activity may, in part, account for certain behavioral changes observed in those affected by SAD (Depue and Iacono, 1989; Lam et al., 2001).

In an animal study of female sheep, it was shown that the seasonal inhibition of luteinizing hormone (LH) involves the activation of monoaminergic and especially dopaminergic systems (Thiéry et al., 2002). In human studies, findings of lower serum prolactin levels and higher eye blink rates in winter and summer support the occurrence of changed dopaminergic function in SAD (Depue et al., 1990). Reduced heat-loss responses to thermal challenge in winter indicative of a lower dopaminergic tone have also been observed in some studies (Arbisi et al., 1989). A [^{123}I] β-CIT single photon emission computed tomography (SPECT) study showed a reduction in the striatal density of dopamine transporter availability in drug-free, symptomatic depressed SAD patients in comparison with healthy controls (Neumeister et al., 2001).

Negative findings include normal levels of catecholamine metabolites in the cerebrospinal fluid (CSF) of SAD patients before and

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; CSF, cerebrospinal fluid; IBZM, [^{123}I] iodo-benzamide; LH, luteinizing hormone; MINI, Mini International Neuropsychiatric Interview; ROI, regions of interest; SAD, seasonal affective disorder; SPECT, single photon emission computed tomography; SD, standard deviations.

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after light therapy (Rudorfer et al., 1993). In addition, a double-blind study showed that the administration of a combination of levodopa and carbidopa was not superior to a placebo in patients with SAD (Oren et al., 1994).

Controversy exists regarding the role of brain dopamine in seasonality, and there is a lack of data on the seasonal changes of human striatal dopamine D_2/D_3 receptor availability in healthy individuals. In this study, through the exploration of the differences in striatal dopamine D_2/D_3 receptor availability in the human brain between participants exposed to higher and lower amounts of sunshine using SPECT with [^{123}I] iodo-benzamide (IBZM), we aimed to explore the relationship between sunshine exposure and striatal dopamine D_2/D_3 availability.

2. Methods

2.1. Subjects

The participants ($n=68$, 43 males and 25 females) were recruited from the community through research advertisement between 1999 and 2005 in Taiwan and were enrolled in various studies as healthy controls. Their mean age was 33 years (standard deviation (SD) = 12.03). The participants' health was checked by a physician, and experienced psychiatrists used the Chinese version of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to exclude individuals with any psychiatric disease. Any history of smoking, alcohol intake, and exercise in the participants was recorded; all were free from the use of any medications or illegal substances and all refrained from caffeine and alcohol use on the day of the study. Informed consent was obtained from all study participants. The study protocols were approved by the Ethical Committee for Human Research in the National Cheng Kung University Hospital.

Taiwan is in a subtropical area (120°12′ 17″E, 22° 59′ 36″ N) which experiences only small seasonal changes, and the duration of sun exposure between the seasons does not vary as dramatically as in northern Europe. The sunshine-exposure data used in this study were not calculated on the basis of traditional seasonal changes but on the duration of sunshine during the 30 days before the day of study (data obtained for 1999–2005 from the Central Weather Bureau in Taiwan). The sunshine exposure of all 68 subjects appeared to be of a normal distribution; those who scored in the upper and the lower quartiles of the distribution were defined as belonging to high- and low-sunshine-exposure subgroups, respectively.

2.2. Image analysis

SPECT scanning with [^{123}I]-IBZM was used to measure striatal D_2/D_3 receptor binding. Each subject was intravenously administered 185 MBq (specific radioactivity 8900 MBq/nmol) of [^{123}I]-IBZM (Institute of Nuclear Energy Research, Lungtan, Taiwan) in a quiet environment about 10 min after inserting the intravenous lines. Imaging was initiated approximately 120 min later by a triple-headed rotating gamma camera (Multispect 3, Siemens). The reconstructed transverse images were aligned parallel to the canthomeatal line. The slice thickness of each transverse image was 2.89 mm.

The detailed imaging measurement procedure was as described in our previous paper (Chen et al., 2005). In brief, regions of interest (ROI) were placed over the striatum and the frontal cortex: an experienced nuclear medicine specialist who was blind to the subjects' data drew the ROIs manually based on individual MRI scans. The ratio of the radioactivity in the striatum (St) and frontal cortex (F) (the St/F ratio) was then derived by dividing the average counts per pixel in the striatum by the average counts per pixel in the frontal cortex.

2.3. Statistical analysis

The data were analyzed using SPSS software (SPSS15 Inc. Chicago, IL, USA). Means and SD were calculated for descriptive analysis of participants' age, sex, smoking status, duration of sun exposure and average temperature during the 30 days before the day of the image study, and striatal dopamine D_2/D_3 receptor availability. Independent t tests and x^2 tests were used to examine the differences between the high- and low-sunshine-exposure subgroups.

Because age and body mass index (BMI) could both confound analysis of the difference in striatal D_2/D_3 receptor availability between the high- and low-sunshine-exposure subgroups (Volkow et al., 1998; Wang et al., 2001), stepwise linear regression was used to identify the main factor for our samples. Additionally, sex and smoking status differed between the two groups, and therefore analysis of covariance (ANCOVA) was used to control for sex, smoking status, and age (or BMI). We also performed partial correlation analysis, controlling for sex, smoking status, and age (or BMI), of the association between striatal D_2/D_3 receptor availability and sunshine exposure. The threshold for statistical significance was established at $p<0.05$.

3. Results

The striatal dopamine D_2/D_3 receptor availability of participants in the low- ($n=18$) and high-sunshine-exposure ($n=17$) groups were compared, a total of 35 patients, 23 males and 12 females, with a mean age of 32.26 (SD = 12.46) years. The demographic data of the groups are shown in Table 1. The result of stepwise linear regression indicated age to be the main factor ($p=0.00$), rather than BMI ($p=0.13$). After controlling for age, sex and smoking status, the difference in striatal D_2/D_3 receptor availability between the high- and low-sunshine-exposure subgroups was significant ($F=7.97$, $p=0.00$), and the result of partial correlation analysis was also significant ($r=0.30$, $p=0.02$).

In the low-sunshine-exposure group, 56% of the SPECT studies were performed in December and January, in contrast with the studies of the high-sunshine-exposure group, 71% of which were performed in March and September. The duration of sunshine was significantly correlated with the average temperature during the 30 days before the day of the image study ($r=0.29$, $p=0.02$), and the average temperature during the 30 days before the day of the image study in the high-sunshine-exposure group was greater than that in the low-sunshine-exposure group.

4. Discussion

The largest difference in the duration of sunshine exposure between summer and winter is approximately 2.5 h per day in Taiwan, a subtropical country, which is significantly lower than in regions of higher altitude (e.g., >13 h difference per day in the duration of sunshine exposure between summer and winter in Finland (Koskela et al., 2008). The result of the current study indicates that striatal dopamine D_2/D_3 receptor availability may be sensitive to sunshine-exposure variations, even in subtropical areas.

Dopamine is the major retinal transmitter involved in the light response, and light therapy might therefore be used to treat SAD by stimulating the production of retinal dopamine and suppressing the production of retinal melatonin (Hébert et al., 2004; Oren, 1991). The specific binding of [^{3}H] spiperone, a D_2 dopamine receptor ligand, in the retinas of rabbits kept for one week under constant light was significantly lower than that of rabbits maintained under constant darkness (Dubocovich et al., 1985). In another study of rats adapted for 3 weeks to lighting programs, dopamine levels peaked during the dark phase of both illumination cycles in the corpus striatum (Friedman and Piepho, 1979). In light of the results of animal studies,

Table 1
Demographic characteristics of the participants: mean values (SD).

	High-sunshine exposure ($n=17$) Mean (SD)	Low-sunshine exposure ($n=18$) Mean (SD)	Statistical test $t/F/x^2$
Age (years)	31.59 (13.50)	32.89 (11.75)	−0.31
Sex (male/female)	15/2	8/10	7.44**
Smoker (yes/no)	9/8	3/15	5.11*
BMI	24.49 (2.38)	21.61 (3.42)	2.04
HDRS	2.00 (2.89)	3.50 (2.79)	−1.15
Duration of sunshine exposure (hours/30 days)	193.08 (5.89)	136.38 (9.59)	20.93**
Temperature (°C)	24.41 (4.49)	21.21 (3.35)	2.38*
Striatal D_2/D_3 receptor availability, St/F ratio	1.98 (0.15)	1.84 (0.21)	7.97**†

*: $p<0.05$; **: $p<0.01$.
†: ANCOVA result, controlling for age, sex and smoking status.
HDRS: Hamilton Depression Rating Scale.

it has been suggested that a sunshine-exposure factor affects striatal dopamine; however, there is as yet no definite evidence of a relationship between the effects of lighting and striatal dopamine. Regarding the finding that a lower striatal D_2 receptor level is a marker of obesity or BMI (Chen et al., 2008; Wang et al., 2001), several researchers have also proposed that a relationship may exist between overeating and low-sunshine exposure (Adam and Mercer, 2004; Scott and Grant, 2006). Therefore, the result of this study could be considered evidence supporting the relationship between lighting and striatum dopamine.

Temperature is another important factor that varies with seasons and was found to be elevated in the high-sunshine-exposure group in the 30 days preceding the trial. Mammals, including humans, maintain internal temperatures within strict limits. Activation of dopaminergic receptors by D_2/D_3 receptor agonists decreases body temperature (Varty and Higgins, 1998), and Millan et al. (1995) also reported that the potency of these agonists to induce hypothermia was correlated more strongly with their *in vitro* affinity for D_3 than D_2 sites. Therefore, the seasonal variation in dopamine D_2/D_3 receptor availability in the healthy human brain observed in this study may not only be associated with sunshine duration but also with temperature and body thermoregulation.

However, the prevalence of major depression and low mood was found to exhibit seasonal variation in a large population-based study, but weather conditions were not observed to be associated with seasonal mood changes (Huibers et al., 2010). In addition, the findings of some studies do not support the involvement of striatal dopamine D_2 receptors in the pathophysiology of major depressive disorder (Hirvonen et al., 2008; Parsey et al., 2001). Therefore, the seasonality of striatal dopamine D_2/D_3 receptor availability may not easily be explained by simple weather or sunshine conditions.

A typical SAD patient is a premenopausal female with a marked craving for high-carbohydrate/high-fat foods resulting in significant weight gain during winter depressive episodes (Kräuchi et al., 1997). Dopamine activity in the meso-cortico-limbic circuitry of the brain has been shown to mediate the rewarding properties of foods (Martel and Fantino, 1996) and body composition (Chen et al., 2008). An association between D_4 receptor and seasonal weight gain in SAD patients was also found in a genetic study (Levitan et al., 2004). Analogous to the seasonal rhythm of brain serotonergic function (Koskela et al., 2008), there may exist seasonal variation in dopaminergic function that is more pronounced in patients with SAD.

It is not clear whether this downregulation of striatal dopamine D_2/D_3 receptors causes an increase in intrasynaptic dopamine or occurs in response to low levels of intrasynaptic dopamine. Previous studies have found that a decline in fine motor activity is highly correlated with decreased striatal D_2 receptor density in patients with schizophrenia (Kuenstler et al., 1999; Yang et al., 2003), and Volkow et al. (1998) demonstrated similar results in healthy subjects. Therefore, lower striatal dopamine D_2/D_3 receptor availability may be viewed as decreasing endogenous dopamine functions and may explain the presence of hypodopaminergic symptoms such as lack of energy, fatigue and overeating in the low-sunshine-exposure group. The findings of the present study were not in agreement with the results of a previous depression study, which showed retardation to be associated with increased striatal IBZM (Shah et al., 1997). One explanation for the discrepancy between the two studies may have arisen from the different groups of participants. Neumeister et al. (2001) showed a reduction in the availability of striatal dopamine transporter availability binding sites in patients with SAD, a specific subtype within the depression spectrum that affects only a minority of depressed patients.

The results of the present study need to be interpreted with caution owing to the following limitations: 1) Our study examined different subjects at varied time points. It is important to perform within-subject comparison in further studies. 2) The demographic distributions of sex and tobacco use differ in the high- and low-sunshine-exposure groups. The inequality might influence the correlation and readers need to notice the possibility of gender differences corresponding to seasonal effects and smoking differences in respect to dopaminergic parameters. However, the lack of gender variation in striatal dopamine D_2 receptor binding observed in this study is consistent with the results of other studies (Munro et al., 2006; Parellada et al., 2004), and the observation of no differences between smokers and non-smokers was similar to the findings in our previous study (Yang et al., 2008). 3) The relatively small size of the sample of individuals recruited from the community analyzed in this study limits generalization of the results. 4) Only healthy subjects were recruited, and we are not sure how differences in sunshine exposure might affect people with mental illness. 5) Variation in the tracer binding potential following changes in central dopamine levels might not be fully captured by a simple density model such as that used in this study (Laruelle, 2000).

In conclusion, this study documents increased striatal dopamine D_2/D_3 receptor availability in the high-sunshine-exposure subjects in comparison with the low-sunshine-exposure subjects, which suggests that the central dopaminergic system may play a role in the neurobiological characteristics of seasonality.

Conflict of interest

All authors declare that they have no conflict of interest. The funding institutions of this study had no further role in the study design; the collection, analysis and interpretation of data; the writing of the report; or the decision to submit the paper for publication.

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