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Seasonality of striatal dopamine synthesis capacity in Parkinson's disease

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HIGHLIGHTS

- PET was used to measure brain dopamine synthesis capacity in Parkinson's disease.
- Two independent seasonal oscillations were seen in the striatal dopamine system.
- Winter and spring births were associated with increased striatal dopamine synthesis.
- Fall and winter scans showed increased right putaminal dopamine synthesis capacity.

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ABSTRACT

Recent neuroimaging evidence suggests that the healthy human brain dopaminergic system may show seasonal rhythmicity, as striatal dopamine synthesis capacity has been reported to be higher during fall and winter. There is additional evidence about season of birth effects on morbidity in several neuropsychiatric disorders. We investigated possible seasonal changes in dopamine synthesis capacity in a relatively large sample of Parkinson's disease patients. 6-[^{18}F]fluoro-L-DOPA brain PET scans for 109 Parkinson's disease patients were performed during different seasons and the effects of season of scanning and season of birth on striatal tracer uptake were studied, controlling for covariates such as age, sex and disease severity. The patients scanned during fall and winter had 15% higher tracer uptake in the right putamen compared to patients scanned during spring and summer ($p = 0.04$). Patients born during winter and spring had 10% higher dopamine synthesis capacity in the left caudate ($p = 0.008$), 8% higher capacity in the right caudate ($p = 0.04$) and 16% higher capacity in the putamen contralateral to the side of predominant motor symptoms ($p = 0.02$) compared to patients born during summer and fall (after correcting for differences in age, sex, disease severity, scanner and season of scanning). The results suggest that there are seasonal oscillations also in the hypoactive dopaminergic system of Parkinson's disease patients. Findings concerning season of birth further suggest that there may be gestational or perinatal seasonal factors, which influence dopaminergic function in adulthood.

1. Introduction

It has been claimed that circannual rhythmicity of seasons has effects on epidemiology or symptoms of several neurological and psychiatric disorders. In addition to seasonal affective disorder, a specific mood disorder occurring in winter with a remission the following spring/summer [24], also certain neurological disorders, such as multiple sclerosis [3,12,15] and ischemic strokes [23], show seasonal variation in activity or symptom presentation. Season of birth is another aspect of seasonal oscillations, with the assumption that there are gestational or perinatal factors that could influence morbidity in adulthood. The most convincing data about season of birth effects has been reported in schizophrenic patients. In a systematic meta-analysis of northern hemisphere season of birth studies in schizophrenia, a significant excess for winter/spring births has been seen together with variation according to latitude [5]. Studies in substance abuse [11], epilepsy [20], multiple sclerosis [25], amyotrophic lateral sclerosis [21] and narcolepsy [4] have also indicated differences in the seasonality of birth when compared to the general population. However, studies in Parkinson's disease (PD) have indicated no circannual changes in motor symptom severity, when measured with the Unified Parkinson's disease Rating Scale (UPDRS) [17]. The season of birth studies in PD have suggested either an excess of winter and spring births [21], only

Abbreviations: PD, Parkinson's disease; PET, positron emission tomography; UPDRS, Unified Parkinson's disease Rating Scale; FDOPA, 6-[^{18}F]fluoro-L-DOPA; LEDD, levodopa equivalent daily dose.

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trend level similar effect of season of birth [7,10], or no effect of season of birth on PD risk [14,18].

Positron emission tomography (PET) provides a means to investigate possible seasonal variation in neurotransmission directly from the brain in vivo. Human brain serotonin transporter binding has been reported to show seasonal variation, as evidenced by [^{11}C]DASB PET, with higher serotonin transporter density and lower synaptic serotonin levels in the fall and winter [19]. In the dopamine system, significant sunshine-exposure variation of human striatal D_2/D_3 receptor availability has been reported in a subtropical region [22]. The recent results by Eisenberg and colleagues indicated that, in healthy human subjects, the presynaptic dopaminergic system, as measured with 6-[^{18}F]fluoro-L-DOPA (FDOPA) PET, shows seasonal variation with higher uptake values during fall and winter (fall equinox to spring equinox) compared to spring and summer [8]. The findings by Eisenberg et al. are of interest to researchers investigating disorders of dopamine, such as schizophrenia and PD. If there is indeed clinically significant seasonal variation in the dopamine system, it could influence the interpretation of clinical diagnostic dopaminergic neuroimaging, treatment, symptoms and even the quality of life of the patients, although, as pointed out above, there is no clear clinical evidence of such seasonal oscillations in the case of PD. Importantly, as detailed above, there are some previously reported neuroimaging studies about seasonal fluctuations in neurotransmitter function [8,19,22], but there are no previous functional brain imaging studies about season of birth.

In the present study, our first aim was to replicate the findings by Eisenberg et al. of seasonal variation in FDOPA uptake [8], in a relatively large sample of patients with idiopathic PD. Our second aim was to investigate possible effects of season of birth on basal ganglia dopamine function.

2. Materials and methods

The sample included 109 Caucasian patients with PD (mean age = 63.1 years, SD = 8.3, range 38–80 years, 29 women and 80 men) who were scanned with FDOPA for clinical PD neuroimaging projects at the Turku PET Centre, Finland. The scanning of the sample had been performed evenly during different months (December–January $n = 17$, February–March $n = 20$, April–May $n = 19$, June–July $n = 11$, August–September $n = 15$, October–November $n = 27$). All patients were born in Finland during the years 1920–1965. Eighty-nine patients were drug naïve at the time of scanning (disease duration <5 years) and 20 patients were receiving antiparkinsonian medications (in medicated patient: mean total LEDD = 686 mg, SD = 228, range 210–1127 mg). In the medicated patients, dopaminergic drugs were discontinued for a minimum of 12 h before scanning (minimum of 24 h for slow-release medications). The scanning was performed between 9 am and 5 pm. The severity of PD was assessed at the PET Centre on the day of the scanning according to the motor part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS) (mean score = 30.0, SD = 9.6, range 8–52). The predominant side of the motor symptoms was left in 65 patients, right in 43 patients and symmetrical bilateral in one patient. All participants gave their informed consent and the ethical committee of the Turku University Hospital approved the studies. The study was conducted according to the principles of the Declaration of Helsinki.

The radiochemical synthesis of FDOPA was carried out as described earlier (Forsback et al., 2008). The radiochemical purity exceeded 98% in every case. Dynamic 90-min 3D scans (frames: 15× 1 min, 5× 3 min, 12× 5 min) were performed with either a GE Advance ($n = 89$) (General Electric Medical Systems, Milwaukee, WI, USA) or with an ECAT EXACT HR+ ($n = 20$) (CTUSiemens, Knoxville, TN, USA) PET scanners. Each subject also underwent a 1.5 T MRI scan for anatomical reference and to exclude clinically significant structural lesions (Siemens Magnetom, Erlangen, Germany or Philips Gyroscan Intera CV Novo Dual scanner, Best, The Netherlands). Each patient received 150 mg of carbidopa 1 h before the injection of FDOPA. Before scanning, an antecubital vein was cannulated, and a rapid i.v. bolus of FDOPA [mean = 175.9 MBq, SD = 20.6, range 113–213 MBq) was given at the beginning of the PET scan. A vacuum hood or a Velcro strap was used to reduce head movements during scanning. Regions of interest (bilaterally the dorsal caudate nucleus, the putamen, and the occipital cortex) were delineated on individual coregistered MRIs using Imadeus software (Version 1.20, Forima Inc., Turku, Finland). FDOPA uptake was studied separating the left/right hemispheres and the contra-/ipsilateral hemispheres to the predominant symptoms of PD. K_i^{ref} values representing the uptake of FDOPA were calculated using a graphical analysis of data from 15 to 90 min from injection using the occipital cortex as the reference region [16].

For statistical analysis, the patients were separated into groups according to season of scanning and season of birth. For season of scanning, we used equinox-to-equinox periods similarly to as Eisenberg et al. (Fall-Winter = September 23rd to March 20th; Spring-Summer = March 21st to September 22nd) [8]. Since the evidence concerning season of birth effects in neuropsychiatric disorders, particularly in schizophrenia and PD, is weighted to Winter–Spring vs. Summer–Fall (solstice to solstice) [5,21], we used solstice-to-solstice periods of the astronomical year for seasons of birth (Winter–Spring = December 22nd to June 21st; Summer–Fall = June 22nd to December 21st).

The statistical computations were performed with PASW Statistics (version 18.0, SPSS Inc., Chicago, IL, USA). The normality of the distributions was evaluated using Shapiro–Wilk or Kolmogorov–Smirnov tests and visual inspection of the histograms. The differences between K_i values were investigated with ANOVA using age, sex, UPDRS part III score, scanner and season of birth/season of scanning as covariates. Student's *t*-tests, Mann–Whitney *U*-tests or Fisher's exact tests were used for demographic variables when appropriate. The same statistical criteria was used as in the study by Eisenberg et al., and *p*-values less than 0.05 were interpreted as statistically significant.

3. Results

Patients scanned during fall and winter (September 23rd to March 20th, equinox to equinox) had a 15.1% higher uptake in the right putamen compared to patients scanned between March 21st and September 22nd after controlling for covariates ($F = 4.52$, df = 108, $p = 0.036$) (Table 1). No significant differences were seen in other studied brain regions (Table 1).

Patients born during winter and spring (December 22nd to June 21st, solstice to solstice) had 9.5% higher FDOPA uptake in the left caudate nucleus compared to patients born between June 22nd and December 21st ($F = 7.28$, df = 108, $p = 0.008$) (Table 2). The difference was also significant in the contralateral putamen (16.1% difference, $F = 6.16$, df = 108, $p = 0.015$) and the right caudate (8.2% difference, $F = 4.15$, df = 108, $p = 0.044$). The differences were also seen without any covariates (independent samples *t*-test, Winter–Spring vs. Summer–Fall: contralateral putamen, $t = 2.16$, df = 107, $p = 0.033$; contralateral caudate, $p = 0.030$), and when only scans from the GE Advance scanner and unmedicated patients ($n = 89$) were used in the analysis (contralateral putamen, Winter–Spring vs. Summer–Fall, $F = 5.53$, df = 88, $p = 0.021$; contralateral caudate, $F = 6.24$, df = 88, $p = 0.014$; age, sex, UPDRS part III score and season of scanning used as covariates).