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ORIGINAL PAPER

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Converging evidence suggests that monoamine neurotransmitter turnover in human adults is associated with their season of birth

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Abstract Separate studies on adults, including those in suicidology and another regarding personality in the general population, have indicated associations with their season of birth. We analyse each of these studies by multiple nonlinear regression employing a cosine function for the month of birth, and compare these studies regarding the birth months giving the maxima and minima. The method of suicide in suicide studies shows a significant month-of-birth variation similar to that for the serotonin metabolite 5-HIAA in the separate study on cerebrospinal fluid, with a peak around the birth month September and a nadir around birth in March. When comparing the personality study with the study on cerebrospinal fluid, the trait novelty seeking varies similar to that for the dopamine metabolite HVA or the norepinephrine metabolite MHPG, and the trait reward dependence varies similar to that for HVA. The trait self-transcendence varies similar to the ratio of the dopamine and serotonin metabolites. Dopamine turnover in adults thus shows a peak around the birth months November-December, and a nadir around the birth months May-June, suggesting a possible involvement of the length of photoperiod during their perinatal period. These results provide strong evidence for the influence of season of birth on adult monoamine neurotransmitter turnover, and give further support for the monoaminergic modulation of the temperament and character traits.

Key words Season of birth · serotonin · dopamine · norepinephrine · personality · suicide method

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Introduction

Season of birth is known to be associated with several psychiatric and neurological disorders in adults (Torrey et al. 1997). Other season-of-birth associations have also been reported. For example, population studies regarding adult life expectancy have shown that those born in the northern hemisphere during October to December live longer than those born during April to June, and the pattern is shifted half a year in the southern hemisphere (Doblhammar and Vaupel, 2001). This suggests that the circumstances around the gestational and perinatal period may be modulating several neurodevelopmental aspects, likely involving also the development of the monoamine neurotransmitter systems, with long-term effects extending into adulthood.

The rate of turnover of the monoamine neurotransmitters dopamine, serotonin, and norepinephrine in the central nervous system are known to be influenced by genetic as well as environmental factors (Clarke et al. 1996; Higley et al. 1993; Schneider et al. 1998; Reznikov et al. 1999; Herlenius and Lagercrantz 2001). Since cerebrospinal fluid (CSF) levels of their metabolites homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), and 3-methoxy–4-hydroxyphenylglycol (MHPG), respectively, are generally positively correlated with the turnover of the corresponding monoamines, these levels are often used as indicators of their turnover.

It was found in a clinical sample of adult patients with the psychiatric diagnoses of mood, anxiety, or adjustment disorder, that their CSF levels of the metabolites 5-HIAA and HVA showed an association with their season of birth (Chotai and Åsberg 1999). Those born during February to April had significantly lower levels of 5-HIAA, and those born during October to January had significantly higher levels of HVA, as compared to birth during the rest of the year.

In another study analysing a register of completed suicides during the period 1952–1993 from another part of Sweden, it was found that those born during February to April had employed significantly more often hanging as the suicide method rather than poisoning or petrol gases. Those born during October to January had employed hanging significantly less often (Chotai et al. 1999). Further analyses of this register in relation to any previous contact with psychiatric services suggested that most likely the association between the method of suicide and the season-of-birth was mediated independently of any serious psychiatric illness, through a season of birth variation in some vulnerability or diathesis for suicidal behavior, probably the serotonergic system (Chotai and Salander Renberg 2002).

Season of birth has also been reported to be associated with personality evaluated by the temperament and character inventory (TCI; Cloninger et al. 1993) in a general population (Chotai et al. 2001). Those born during February to April were significantly more likely than those born during October to January to have high NS (novelty seeking) among women, in particular the subscale NS2 (impulsiveness vs. reflection), and to have high PS (persistence) among men. The dopaminergic system is known to be involved in brain reward mechanisms, and some associations between the dopaminergic system and novelty seeking have been reported in the literature (Ebstein et al. 2000; Gerra et al. 2000).

In the present study, we compare the results in the above papers with each other by means of multiple nonlinear regression analyses involving a cosine function of the month of birth, to explore eventual common features or explanations regarding the association between the monoamine neurotransmitter turnover in adults and their season of birth.

Subjects and methods

Subjects and studies

The study by Chotai and Åsberg (1999) contains data on CSF levels of the monoamine metabolites HVA, 5-HIAA and MHPG for a clinical sample of 241 adults (65% women) from Stockholm, middle Sweden, with the psychiatric diagnoses of mood, anxiety, or adjustment disorder. The study by Chotai et al. (1999) contains data on the suicide methods employed by 1466 victims (24% women) in the complete register of suicides during the period 1952–1993 in the county of Västerbotten, northern Sweden. The study by Chotai et al. (2001) on a general population cohort of 2130 individuals (56% women) in Umeå, northern Sweden, contains responses to Cloninger et al. (1993) self-report temperament and character inventory of personality (TCI), consisting of the four temperament traits of novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS), and the three character traits of self-directedness (SD), cooperativeness (C), and self-transcendence (ST).

Statistical analyses

We employ multiple nonlinear regression as below to fit a cosine function to each of the above situations for variation according to the month of birth, and compare the birth months yielding the maxima and minima of the cosine function across the different situations.

In the situation where the CSF level of a monoamine metabolite varies according to the month of birth, we employ this level as the dependent variable, and model for the independent variables consisting of gender, age, and a cosine function of the month of birth, exemplified for HVA as follows:

$$HVA = M + A \cos(0.5236\, t + F) + B\, x + C\, y$$

where t denotes the month of birth (Jan = 1, Feb = 2, ..., Dec = 12), x denotes gender, and y denotes age in years. The coefficient of t is given by 2π divided by the total period of 12 months, which gives $2\pi/12 = 0.5236$. The regression analysis estimates the parameters M, A (amplitude), F (phase angle), B, and C. The cosine fit is considered to be statistically significant when the amplitude A is significantly different from zero. The birth month t_{max} giving the maximum and the birth month t_{min} giving the minimum of the cosine curve are calculated by the expressions $-F/0.5236$ and $(\pi - F)/0.5236$.

In the situation concerning the method of suicide, for example, hanging, the dependent variable consists of the percentage employing hanging within all those suicide victims born during a particular month t. This is accomplished by coding the dependent variable as 100 if hanging was employed and 0 otherwise. The independent variables consist of gender, age, and the cosine function of t.

In the situation concerning each of the personality traits, for example, NS, the dependent variable consists of the value of NS obtained. The independent variables comprise gender, age, the month of TCI evaluation, and the cosine function of the birth month t.

Results

Tables 1–3 show the results for the cosine amplitude A, and whenever it is significantly different from zero either for the total sample or for any of the genders, we also give the corresponding birth months t_{max} and t_{min}.

A figure showing the curves for the month of birth variation of the CSF monoamine metabolites has been published earlier (Chotai and Åsberg 1999). The results of our analyses of these data are given in Table 1. The cosine amplitude was significant for HVA with maximum around November–December (t_{max} around 11–12) and

Table 1 Estimates of the amplitude A of the cosine curve according to the month of birth, and the birth months giving the maximum and the minimum of the curves

	Both genders pooled			Women			Men		
	A	t_{max}	t_{min}	A	t_{max}	t_{min}	A	t_{max}	t_{min}
CSF monoamine metabolites: clinical sample in Stockholm, Sweden (241 subjects)									
HVA	16.2*	11.0	5.0	16.2	10.5	4.5	17.8	11.6	5.6
5-HIAA	7.9*	9.4	3.4	5.0	9.8	3.8	13.1**	9.2	3.2
MHPG	2.3*	10.3	4.3	1.7	10.6	4.6	3.2*	10.2	4.2
HVA/5-HIAA	0.2**	1.2	7.2	0.2	11.7	5.7	0.4**	2.3	8.3
HVA/MHPG	0.3			0.3			0.3		
5-HIAA/MHPG	0.1			0.0			0.2		

* $p < 0.05$; ** $p < 0.01$

Table 2 Estimates of the amplitude A of the cosine curve according to the month of birth, and the birth months giving the maximum and the minimum of the curves

	Both genders pooled			Women			Men		
	A	t_{max}	t_{min}	A	t_{max}	t_{min}	A	t_{max}	t_{min}
Method of suicide: register of all suicides in the county Västerbotten, northern Sweden, 1952–1993 (1466 cases)									
Hanging (%)	5.4**	3.1	9.1	4.0	2.7	8.7	5.8**	3.0	9.0
Poisoning/ petrol gases (%)	4.5**	9.3	3.3	5.6	1.4	7.4	4.9**	9.8	3.8

**$p < 0.01$

Table 3 Estimates of the amplitude A of the cosine curve according to the month of birth, and the birth months giving the maximum and the minimum of the curves

	Both genders pooled			Women			Men		
	A	t_{max}	t_{min}	A	t_{max}	t_{min}	A	t_{max}	t_{min}
TCI personality scales: population cohort in the town Umeå, northern Sweden (2130 subjects)									
NS (novelty seeking)	0.32[a]	4.7	10.7	0.48*	4.7	10.7	0.11	4.6	10.6
HA (harm avoidance)	0.10			0.10			0.24		
RD (reward dependence)	0.42*	5.9	11.9	0.21	6.5	12.5	0.29	5.4	11.4
PS (persistence)	0.09			0.13			0.13		
SD (self-directedness)	0.07			0.07			0.24		
C (cooperativeness)	0.10			0.26			0.15		
ST (self-transcendence)	0.43*	1.4	7.4	0.50	12.0	6.0	0.64*	2.7	8.7

[a]$p = 0.055$; *$p < 0.05$

minimum around May–June (t_{min} around 5–6). For 5-HIAA, it was particularly significant for males, with the maximum around September and the minimum around March. For MHPG also, it was particularly significant for males, with the maximum around October and the minimum around April.

The results of analysing the data on completed suicides from Chotai et al. (1999) are given in Fig. 1 and in Table 2. The month of birth that gave the highest percentage of suicide by hanging and the lowest percentage of suicide by poisoning or petrol gases was around March, particularly significant for males. The month of birth having the converse preference for the suicide methods was around September.

The results of analysing the data on the seven personality traits of the TCI in a general population from Chotai et al. (2001) are given in Fig. 2 and in Table 3. The first four traits in the table are those of temperament and the last three are the character traits. Novelty seeking scores show a maximum for the birth month around

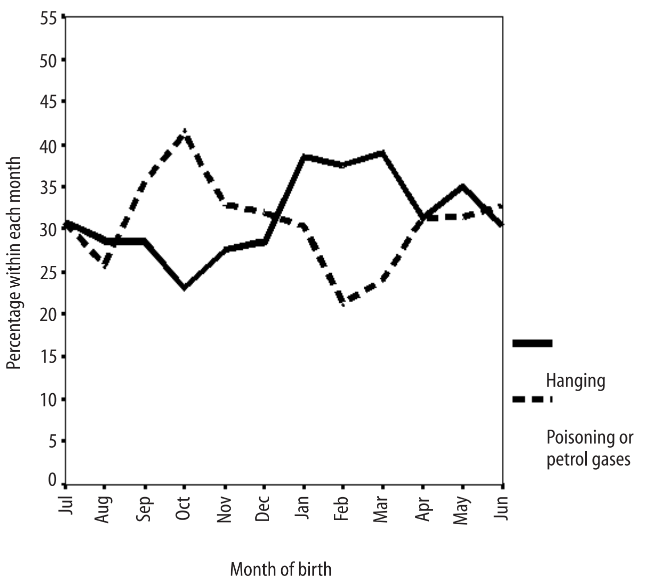

Fig. 1 The method of suicide according to the month of birth for the register of 1466 suicide victims in Chotai et al. (1999). The curves give the percentage employing hanging or poisoning/petrol gases among all those born during the given month

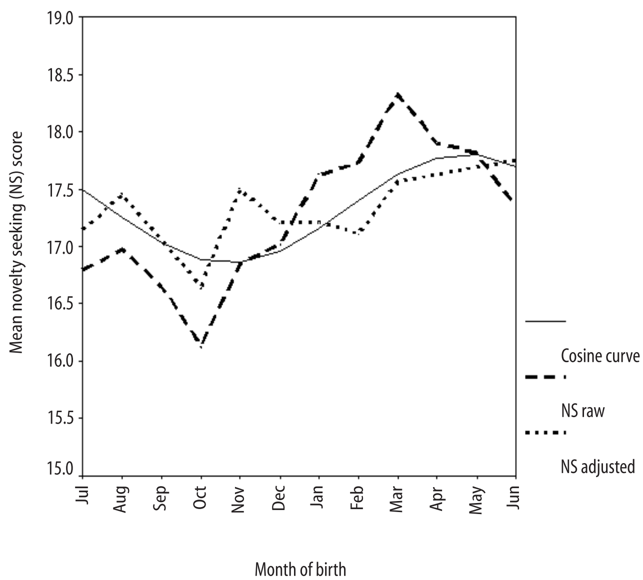

Fig. 2 Novelty seeking scores according to the month of birth for the 2130 subjects in the population cohort in Chotai et al. (2001). The curves give the mean raw NS scores, the NS scores after adjusting for age, gender and the month of TCI measurement, and the cosine curve obtained by nonlinear regression

April–May ($t_{max} = 4.7$) and a minimum for the birth month around October–November ($t_{min} = 10.7$). Reward dependence shows a maximum for the birth month around May–June ($t_{max} = 5.9$) and a minimum for the birth month around November–December ($t_{min} = 11.9$). Self-transcendence shows maxima and minima at months of birth that are different for the two genders.

Discussion

We employed a cosine function of the month of birth as one independent variable and adjusted for the other independent variables like gender and age by multiple nonlinear regression. The dependent variables in turn included the levels of the CSF monoamine metabolites from one study (Table 1), the percentage employing a particular method of suicide from another study (Table 2), and the seven personality traits of the TCI in a third study (Table 3).

Comparing Table 2 on suicide with Table 1, the neurotransmitter that gave a month of birth variation similar to that for the suicide methods was the serotonin metabolite 5-HIAA. Our result indicates a parallel between preference for hanging and lower serotonin turnover, and between preference for poisoning or petrol gases and higher serotonin turnover. This is in line with the literature suggesting an involvement of serotonin in aggressiveness and in suicidal behavior (Åsberg 1997; Mann 1998). Our result thus adds further credibility to the hypothesis of a variation in adult serotonin turnover according to their season of birth.

Comparing Table 3 on personality with Table 1, novelty seeking scores show a maximum for the birth month around April–May, corresponding to low norepinephrine metabolite MHPG or low dopamine metabolite HVA, and conversely for the birth month around October–November. Reward dependence shows a maximum around May–June, corresponding to low dopamine metabolite HVA, and conversely for the birth month around November–December. These results may be due to the following. Some evidence in the literature suggests that both dopamine and norepinephrine may be associated with the traits of novelty seeking and reward dependence, and that these traits may be somehow related with each other as regards the biochemical background (Gerra et al. 1999; Gerra et al. 2000). Genetic evidence in the literature also suggests that specific personality traits may involve specific ratios of functionally related groups of genes, and different genotypes of the same genes may underlie different personality traits (Ebstein et al. 2000; Comings et al. 2000 a).

The character trait of self-transcendence in Table 3 shows a significant cosine amplitude with maxima and minima at different months of birth for males as compared to those for females or for the pooled sample. Comparing this with Table 1, we find that this pattern is similar to that obtained by the variation in the ratio HVA/5-HIAA, which reflects a month-of-birth variation in the degree of interaction between dopamine and serotonin. Self-transcendence has shown an association with the dopaminergic activity through its association with the D4 receptor gene DRD4 (Comings et al. 2000 b). In Cloninger's model of the TCI (Cloninger et al. 1993), the character traits are assumed to be weakly heritable and moderately influenced by social learning, and depend on the individual's social values and goals. Interactions between different neurotransmitter systems may thus underlie such processes.

In summary, we have found significant evidence from individual studies investigating the role of season of birth in suicidology and in personality, respectively, that their month-of-birth cosine curves reach the maxima and minima similarly to those of the cosine curves of specific CSF monoamine metabolites or their ratios in another study. Month-of-birth variation for the method of suicide follows the pattern of the serotonin metabolite, and month-of-birth variations for personality traits follow the patterns of the dopamine or the epinephrine curves, or of the curve of the ratio between the dopamine and serotonin metabolites. The development of personality, including the character traits, is likely to parallel the development of the turnover of monoamines, and their interactions, in the brain.

Thus, our study strongly suggests that the rate of turnover of the monoamines in adults is in part related to circumstances around their season of birth. The season of birth is an unspecific indicator of the season of conception, the season of gestation, and the season of the immediate postnatal life. Dopamine turnover in adults shows a peak for those born around November–December, and a nadir for those born around May–June. Dopamine is functionally related to melatonin, since they are both mutually inhibitory paracrine signals for day and night, respectively (Grosse and Davis 1999; Tosini and Dirden 2000). The individual's melatonin rhythm, in its turn, is known to be related to the self-reported morningness-eveningness circadian typology (Duffy et al. 1999; Gibertini et al. 1999). Therefore, a reported association in adults between the circadian typology and season of birth (Natale and Adan 1999; Natale, Adan and Chotai in press), showing a difference between those born during the short photoperiod part of the year compared to those born during the long photoperiod part, further suggests that the season-of-birth association for dopamine turnover in adults may somehow be related to the length of photoperiod during the gestational and perinatal period of these adults.

Generally, the season-of-birth associations may also be related to seasonal non-photic perinatal influences like infections, nutrition, or other seasonal behavioral and stress-related aspects in the parent-offspring interaction. Neonatal infections are known to influence the postnatal development of the brain monoaminergic systems (Pletnikov et al. 2000), and there are several animal studies showing the effects of prenatal stress on the offspring's brain development and function (Lemaire et al.

2000), including that of brain biogenic amines (Schneider et al. 1998; Reznikov et al. 1999; Herlenius and Lagercrantz 2001).

Our study suggests that the turnover of the serotonergic system has a peak for adults born around September and a nadir for those born around March. An indication derived from this is that the turnover of serotonin in adults may be related to non-photic environmental factors rather than the length of photoperiod during the perinatal period. However, this issue is complicated by the fact that the capacity of an environmental factor to influence an embryo depends on whether it exists during conception, during the first trimester, the second trimester, the third trimester, or during the perinatal period. And this may behave differently for different disorders or traits under consideration (Torrey et al. 1997).

So, unless one knows for sure the timing of the embryonic or perinatal critical period that has a bearing on the particular adult trait under study, one cannot resolve what environmental factor underlies a given season-of-birth association. Our study here indicates, however, that there are some environmental factors sometime during conception or during the gestational or perinatal period that have a bearing on adult monoamine neurotransmitter turnover.

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