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Chronomics of autism and suicide

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Abstract

We examine whether autism may be influenced by non-photic environmental factors, among others, in a California database consisting of the number of cases added quarterly to the system between 1993 and 2004. Instead of a precise calendar (1.0)-year-long spectral component, we detect unseen primarily helio- and geomagnetic signatures, including a newly discovered near-transyear of 1.09-year length. In this case, it overrides any undetected seasonal effects, the topic of much previous unrewarding research, also analyzed herein without overcoming the limitation by stacking. Since we could not get additional data on autism, data on suicides, the final “detachment” and failure to bond, were also analyzed, again revealing a spectrum of non-photic signatures. What we do not see and do not anticipate can exist and can override the seasons, as resolved time-microscopically by chronomics, the study of chronomes (time structures). Just as spatial microscopy and electron microscopy resolved infectious agents, so does microscopy in time resolve the signature of environmental agents in human behavior in health and disease.

Keywords

Autism; Chronome; Melatonin; Non-photic cycles; Suicide; Transyear

1. Introduction

Autism is a neurodevelopmental disorder characterized by impairments in reciprocal social interaction, deficits in verbal and nonverbal communication, and a restricted repertoire of activities or interests [1]. Abnormalities associated with autism have been reported [1] in the early development of the amygdala and in the pattern of hippocampal development that persist through adolescence. In order to test whether cell migration and apoptotic mechanisms may account for the observed Purkinje cell abnormalities seen in autism, Fatemi et al. [2] compared Reelin, an important secretory glycoprotein responsible for normal layering of the brain, and Bcl-2, a protein responsible for the coordination of programmed cell death in the brain, between cerebellar cortices of autistic patients and clinically healthy controls matched for gender, age, and post-mortem interval. Both Reelin and Bcl-2 were reportedly decreased in the autistic cerebellum [2]. Blatt et al. [3] also report that the GABAergic receptor system is statistically significantly reduced in high binding regions in autism (see also [4]).

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Dedication

This paper is dedicated to Theo Hellbrügge in appreciation of his invitation to plan a meeting and contribute lectures on this topic and repeated urgings over the telephone to participate in it.

Autism is an etiologically complex disorder with initial presentation in early childhood [5]. It has been characterized by abnormalities in language and social relationships and a repetitive, restricted behavioral repertoire involving reactions to the environment [6]. It has been estimated that over 90% of the etiologic factors are genetic [7], likely of multigenetic etiology [8]. Genetic aspects of the condition were explored by Koczat et al. [5], who report that like the autistic patients, their parents also show poorer spatial accuracy than the control group. Evidence for genetic influences has also been presented by Bolton and Rutter [9], among many others.

Investigators generally agree that a number of genetic infirmities interact with a large number of potential environmental factors to precipitate the brain abnormalities that eventually lead to autism. During the past year, a series of clues have been revealed that point to what may be going wrong in the autistic brain. Courchesne [10] has reported that newborns who later developed autism initially had smaller than normal head circumferences, but within a few months their brains grew more rapidly than normal, so that they had exceptionally large heads during childhood. Herbert et al. [11] have found an excessive early-development of white matter in frontal lobes, cerebellum and association areas, especially in the right hemisphere. Teitelbaum's group [12], through a video-analysis of infantile movement, finds subtle disturbances in early locomotion and head-body coordination that may be of diagnostic value. Just et al. [13] have reported that autistic children remember the alphabet in brain regions that ordinarily processes shapes.

Individuals with autism were found to have statistically significantly lower circulating cortisol and higher circulating ACTH in the morning as compared to controls, in keeping with a dysfunctioning hypothalamo-pituitary-adrenal network in autism [14]. Children with autism were also reported to be more likely to have deficiencies or lower plasma concentrations in essential amino acids [15]. In another study, however, Aldred et al. [16] report that plasma amino acid concentrations such as glutamic acid, phenylalanine, asparagine, tyrosine, alanine, and lysine are higher in autistic patients, their siblings and parents as compared to age-matched controls, supporting the evidence for an underlying biochemical basis for the condition. A possible association between congenital cytomegalovirus infection and autism has been suggested [17]. Phenylketonuria has been noted in children with infantile autism, but its prevalence seems to be very low [18]. Various immune system abnormalities, including autoimmunity and defects in different subsets of immune cells, have been reported in children with autistic disorder, suggesting that immune factors may also play a role in the development of autism [19] (see also [20,21]). There is also abundant evidence suggesting that other peripheral factors may contribute to autistic symptomatology [22].

Whereas some authors suggest that the real incidence of autism has not changed [23], most studies report an exponential increase in recent years [24,25]. Whereas improved methods of early diagnosis may have contributed to the increased reporting of cases of autism, the observed trend has been alarming. California, with a claim to having the world's best record keeping system, is the de facto "canary of the coal mine" in tracking new cases of autism. In 1999, the first California Department of Developmental Services (DDS) report on autism suggested the existence of a growing autism epidemic [24]. A report released by DDS in 2003 documented a doubling of the autism caseload from 1999 to 2002 [26].

2. Materials and methods

Two sets of data are analyzed herein. One set of data stems from the work of Bolton et al. [27] who examined any alterations in the expected seasonal fluctuation in birth dates of autistic people by comparison with the general population. These authors report on a national sample (NAS) of 1435 autistic individuals and a clinic sample of 196 subjects, compared to 121 sibling

controls and the general population of live births in England and Wales. The data, taken from the published article [27], were available as a function of time of birth stacked over an idealized year, and as longitudinal yearly totals covering the span from 1947 to 1979 (33 years). By the stacking, any differentiation between a year and any new transyear is rendered impossible.

From the California database, quarterly trends in the number of persons with autism added to the system since the third quarter of 1993 to the 2nd quarter of 2004 were analyzed. The data consist of the number of new cases per quarter. The quarterly percentage change was also analyzed.

Each data series was analyzed by cosinor, consisting of the least squares fit of cosine functions with anticipated periods. Estimates are obtained for the rhythm-adjusted mean (MESOR), the extent of predictable change within one cycle (double amplitude), and the timing of overall high values recurring in each cycle (acrophase) [28–30]. Because of the large increase in the number of diagnoses, some series were detrended before analysis. This is the case for the California data, recorded as a function of time of diagnosis (or reporting) rather than time of birth. Least squares spectra were also computed in each case to determine any spectral peak indicative of the presence of a periodic component. Nonlinear analyses were further applied to obtain point and 95% confidence interval (CI) estimates of the period [29,30].

3. Results

3.1. Data from Bolton et al. [27]

A circannual variation by month of birth could be demonstrated for the clinic sample of autistic subjects ($P = 0.032$ from the zero-amplitude or no-rhythm test), with a peak in spring and a trough in October, Fig. 1 (upper right). A circannual variation could also be found for live births ($P = 0.017$), with a similar pattern, Fig. 1 (bottom right). The concomitant fit of cosine curves with periods of 0.5 and 0.25 year was found to describe the NAS sample ($P = 0.047$), Fig. 1 (upper left), and cosine curves with periods of 0.33 and 0.2 year modeled the data from siblings ($P = 0.039$), Fig. 1 (bottom left). But all of these analyses are severely limited by the availability only of stacked data.

The main component characterizing the longitudinal series (displayed in Fig. 2) is an about 21-year component, validated by nonlinear least squares. Nonlinearly, a linear trend was fitted together with a cosine function with a trial period of 21 years, anticipated from prior work related to anthropometric measures at birth [31,32]. Results are summarized in Table 1. At the average period of 22.2 years, similar phases are found for the clinic data, the NAS series and live births.

3.2. Data from California

The quarterly numbers of new cases in the California database also showed a sharp increase as a function of time (Fig. 3, upper left). Accordingly, they were fitted with a 3rd-order polynomial, and residuals were used for analysis (Fig. 3, upper right). The data expressed as percentage change did not show any marked increasing trend (Fig. 3, bottom left), and were analyzed as such. Least squares spectra with frequencies in the range of one cycle in 10.5 years (the duration of the observation span) to one cycle in about a year (Nyquist frequency) revealed two components accounting for about 15% of the overall variance for both data series, with periods of about 5 years and slightly longer than 1.0 year. The two-component models resulting from these analyses consist of cosine curves with periods of 5.05 and 1.04 years ($P = 0.026$ and $P = 0.021$, respectively; overall $P = 0.008$) accounting for 30% of the variance in the case of residuals from a 3rd-order polynomial and of cosine curves with periods of 4.62 and 1.09 years ($P = 0.051$ and $P = 0.053$, respectively; overall $P = 0.019$) accounting for 26% of the

variance in the case of the data expressed as percentage change (Fig. 3, bottom right). The 95% CI estimated nonlinearly for the 1.09-year period does not overlap 1.0 year (extending from 1.01 to 1.17 years), but the 95% CIs for the corresponding amplitudes slightly overlap zero, indicating that statistical significance is not reached by nonlinear least squares when the period is considered as a parameter to be estimated.

The data were further stacked over idealized cycles of 1.0 and 1.09 years to visualize the corresponding waveforms and to test the equality of class means by one-way analyses of variance (ANOVA) complementing the analyses by cosinor. Whereas one-way ANOVAs do not find a statistically significant time-of-year effect, a half-yearly pattern, visualized by the bimodal waveform, can be validated by one-way ANOVA, Fig. 4 (bottom). Fig. 4 also shows a relatively smooth cycle with a period of 1.09 years ($P = 0.027$ by cosinor) (top). Cosinor analyses of the four timepoint means rejects the zero-amplitude assumption for the 1.09-year component, but not for the precise 1.0-year cycle. The California database covers a span slightly longer than 10 years, thus allowing an about 0.1-year resolution at a frequency of about one cycle per year (frequency resolution, $\Delta f = 1/T$, where T is length of observation span). The deviation of the near-transyear with a period of about 1.09 year from the precise calendar year of about 1.0 year is thus barely resolved herein.

4. Discussion

Genetic studies of infantile autism have suggested that environmental influences may play an important role in the development of the disorder [33]. Environmental risk factors that may interplay with the internal biological processes were thus sought [34]. Season of birth has been suggested as a potential factor since seasonal variation patterns have long been identified as agents involved in a variety of medical conditions [35,36], including neuropsychiatric disorders [31,32,37–39]. Explanations for a possible seasonality effect include a number of environmental pathogenic influences such as nutritional variations, obstetrical and perinatal complications, viral or other infections, toxins, and temperature fluctuations [27]. Landau et al. [34] reviewed 8 studies since 1981 that examined the relationship between seasonality and autism. In these reports, March and August tended to be associated with an excess incidence while a deficit in autistic births tended to occur in the fall and winter months. Landau et al. [34] point to several methodological issues that need to be considered to interpret the results; In their own study, the control group consists of subjects with mental retardation without autistic features, and the autistic sample includes cases obtained from the international, multi-site field trial used in the development of the definition of autism for DSM-IV [40] as well as consecutive clinic cases, also subcategorizing the sample and control groups into verbal and nonverbal individuals. Despite the large number of cases studied by Landau et al. [34], the patterns sought could not be validated.

The data from the California database, along with other incidence data collected as a function of time are here analyzed for any patterns in time that may shed new light on putative contributing factors underlying the “epidemic” of autism that were previously not considered and that in terms of their cyclicity differ from the seasons.

Limitations of this investigation stem from the relatively sparse data available for analysis and from the drastic trends observed in the last two decades. It should also be realized that some series were available as a function of registration time, whereas others focus on time of birth. Notably since the etiology of autism is not yet understood, it is possible that both time scales may be pertinent. Whether or not this is so, much larger databases are needed to assess the relative contribution from time structures related to time of birth and time of diagnosis/onset (only approximated herein by time of reporting).

The detection of an about 21-year cycle in the data from Bolton et al. [27], and the half-yearly change in the California database may be signatures from non-photoc solar and geomagnetic influences already observed in relation to other medical [41–45] and physical [46–48] data. It will be important to analyze records of original data, rather than of data stacked over anticipated cycles, such as the calendar year, a procedure that best follows a spectral analysis, if and preferably only if a circannual component is present in the spectrum. If another component is detected by spectral analysis, the method here used of stacking the data along the scale of that component's period is applicable, allows further complementary testing and, in the light of such testing, can visualize the component's waveform.

The presence of any half-year component could be checked in another set of data published (as stacked data by calendar month) [34]. The authors compare the incidence of autism and that of mental retardation without features of autism as a function of the month of birth (Fig. 5). A half-yearly component was the most prominent in the spectrum of both conditions, and was detected with borderline statistical significance in a multiple component model including also a 3-month (autism: PR = 68%, $P = 0.061$) or a 4-month (MR: PR = 63%, $P = 0.098$) component in addition to the 6-month component. (Another merit of analyzing unstacked data are the availability of a larger number of degrees of freedom for testing)

A finding of this investigation is the presence of an about 21-year cycle suggesting the influence of non-photoc, perhaps magnetic influences in addition to any photoc influences from the sun on autism. The characteristics of this cycle did not differ, however, from those of the control data, namely live births in England and Wales. An about half-year component remains to be further elucidated. In order to achieve this goal, it will be important to use original data, not stacked over a preconceived interval, and the data would gain from being analyzed both in terms of time of occurrence/diagnosis and in terms of date of birth since the critical time(s) at which any environmental factor may possibly influence the development of autism remain(s) largely unknown.

The detection by meta-analysis in the published data by Bolton et al. [27] of an about 22.2-year cycle, a putative signature of the long-known Hale cycle of sunspot bipolarity [49] is an unspecific hint for those with transdisciplinary interests. There are other Hale-like cycles in motivational behavior [50] as well as in anthropometric measures at birth [41,42]. A half-yearly cycle also apparent in the quarterly changes from California constitutes another signature of environmental magnetoperiodism in biology [45], with melatonin probably involved as a mechanism [51,52] explored in the laboratory and beyond [52–54]. Melatonin has been reported to undergo a half-yearly variation [55], notably at high latitude [56], where effects of geomagnetic disturbances are felt more strongly. It is fitting that Nir et al. [57] reported an abnormal circadian pattern of melatonin in a group of young adults with extreme autism syndrome. Melatonin, excretion, has been shown to decrease in association with geomagnetic storms [58,59]. Most recently, the circadian rhythm of pineal melatonin was found to be not only lowered in its average, the MESOR, but also dampened in its predictable extent of change (circadian amplitude) by a magnetic storm [60]. This study also revealed the involvement of hypothalamic melatonin, with an increased MESOR and amplified circadian variation, as well as that of circulating corticosterone, showing a larger day-to-day variability in association with a magnetic storm [60]. Whether these mechanisms and/or a possibly dampened circaseptan rhythm in melatonin [60] are also involved in autism is now a testable hypothesis.

Endogenous opioid binding to certain (μ) receptors could mediate natural rewards and may underlie an infant's attachment behavior. Moles et al. [61] report that a μ -receptor knockout mouse pup emits fewer ultrasonic vocalizations when removed from its mother but not when exposed to cold or male mouse odor. Other results in this knockout mouse also indicate deficits in attachment behavior. Indeed, molecular mechanisms for conditions characterized by deficits

in attachment behavior, such as an opioid receptor gene [61SSS], deserve continued investigation; but this is best carried out with consideration for a spectrum of magnetoperiodisms analyzed by chronomics that complement genomics [62].

5. Chronome of suicides in Minnesota: proxy for abnormal and possibly unattached behavior

The database on suicide incidence available from the Minnesota Department of Health for the span from 1968 to 2002 (35 years) was analyzed by linear-nonlinear rhythmometry. A least squares spectrum in the frequency range from 1 cycle in 35 years to about 1.2 cycles per year was computed to assess any long-term trends. The data were also analyzed yearly in the frequency range from one cycle per year to about 2 cycles per week, considering each year's data separately. Results were then summarized at each frequency by population-mean cosinor. Nonlinear least squares were used to obtain 95% CI estimates for the spectral peaks, i.e. the periods resolved.

This approach revealed, in addition to a relatively weak circannual variation [63], components with periods of about 1.07 and 1.3 years, corresponding to changes in geomagnetic disturbance and in solar wind speed, among others. These components are validated nonlinearly, with periods estimated as 1.073 (95% CI: 1.053–1.092) years and as 1.293 (95% CI: 1.269–1.317) years, respectively, when fitted concomitantly. The 95% CIs of the corresponding amplitudes do not overlap zero, attesting to the statistical significance of these components. The half-year is also found to be very prominent ($P < 0.001$), indicating that suicides tend to be more frequent around the equinoxes. The circasemiannual amplitude is twice as large as that of the circannual variation ($P = 0.023$). Most prominent is the weekly variation ($P < 0.001$), with a peak incidence on Mondays. The half-week ($P = 0.001$) accounts for the non-sinusoidal waveform.

These added results are in keeping with early reports of a weekly and seasonal variation in suicides [63–65]. The circannual rhythm may relate to the changes in sunshine duration. Seasonal affective disorder, for instance, has been linked to light, being more prevalent in the winter months and at higher latitudes, and being responsive to light treatment. In addition to a photic influence, suicides may also be influenced by non-photic environmental factors, being characterized by a half-year peaking at the equinoxes, a pattern to be compared to that of seasonal affective disorder, and by a far-transyear, with a period of about 1.3 years. A near-transyear candidate warrants further study because it is not validated nonlinearly and may correspond to one of two sidelobes bracketing the year representative of a modulation in amplitude, phase or frequency, with a period of about 11 years. The presence of both a yearly rhythm and of transyears with periods slightly longer than precisely 1.0 year calls for caution in interpreting results covering spans of only one or a few years. These components having similar, but not identical, periods are amenable to beating. In order to resolve various sources of variation, records covering a decade or longer are needed. Managing databases in health departments is an important task that allows the study of putative environmental influences on a long-term basis resolved by chronomics -a chronome (time structure) analysis.

6. Conclusion

Heretofore, the photic and thermic calendar year has been in the focus of scholars interested in autism and suicide. This research has led to such titles as “Season of birth in autism: a fiction revisited”. Herein, focus was extended from any effect of seasons to magnetoperiodisms, including a newly discovered near-transyear, which deserves consideration in the combined molecular and environmental study of behavior in mental health and disease.

The demonstration that a “year” longer than a calendar year—a transyear—fits the data depends upon an appropriate folding of the data in the time domain and constitutes an argument for further large-scale study of the entire partly new spectrum of magnetoperiodisms, with non-specific but persuasive effects that may contribute to autism, among other conditions involving behavior such as suicides [63–66] (see also [67–69]). Unstacked longitudinal data much denser than yearly will be required for an indispensable follow-up, also focusing upon any effects of magnetic storms on autism, e.g. by superposed epochs.

It is noteworthy that cosmic factors involved in suicide have been considered with numerical documentation, albeit without curve-fitting by Emile Durkheim. Detailed statistics are available in a translation by John A. Spaulding and George Simpson, with an introduction by the latter [67]. The effects of latitude, seasonal temperature, time of day and time of week are all considered, and analyses of such data have been published earlier [65]. Durkheim [67] in particular discusses altruistic suicide, suggesting that it is dependent upon the degree of integration into social groups, being common with excessive as well as deficient integration. Our point herein, in Durkheim’s footsteps [67], is that indeed his proposition that cosmic factors contribute another dimension to suicide can be validated in inferential statistical terms, that there is a much broader spectrum of rhythms involved, and that the preoccupation with morals such as that by Masaryk [68] and with other economic considerations such as the contribution by Marx [69] can each be influenced by the time structures of our environment, as resolved by chronomics.

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Fig. 1.

Circannual variation in data from Boiton et al. [27], available as monthly values after stacking over an idealized year. Multicomponent models are fitted to each data set, shown as smooth curves. A circannual variation is detected with statistical significance for the clinic sample of autistic children (upper right) and for live births used as control (bottom right), with high values in spring. Composite models including higher-order harmonics also reach statistical significance for the national sample of autistic children (upper left) and for siblings of autistic children (bottom left). Since the resolution of any underlying transyearly pattern depends upon the analysis of unstacked data and original data were not available from this study, this question was examined in a different data set, as documented in Figs. 3 and 4. © Halberg.

Fig. 2.

Low-frequency changes in yearly data from Bolton et al. [27] available from 1947 to 1979. An about 21-year cycle is detected nonlinearly for each data series, the clinic and national samples of autistic children and live births, used as control. A summary at the average period of 22.2 years (Table 1) reveals a similarity in acrophase among the three sets of data. The signatures of the Hale cycle in health and disease are also time-macroscopically obvious. Since the resolution of any underlying transyearly pattern depends upon the availability of data sampled at a rate higher than twice a year and only yearly values were available from this study, this question was examined in a different data set, as documented in Figs. 3 and 4. © Halberg.

Fig. 3.

Quarterly numbers of new cases of autism in a California database. The increase per quarter shows a large increasing trend (upper left), necessitating the detrending by a third-order polynomial prior to analysis (upper right). The increase in percentage change is much less (bottom left), allowing analysis without any pre-processing. Components with periods of about 5 years and slightly longer than 1-year are found in both data series, as shown for the percentage change (bottom right). A 95% CI can be obtained nonlinearly for the period of each component fitted separately, the latter not overlapping the exact 1.0-year period. While the zero-amplitude test cannot be rejected by nonlinear least squares, by linear least squares as a whole statistical significance is reached ($P = 0.019$), a result prompting further study in Fig. 4. © Halberg.

Incidence of Autism in California (1994-2004) – with Signatures of the Cosmos*

Fig. 4.

Visualization of the near-transyear component detected linearly in Fig. 3 for the quarterly percentage change in new cases of autism in California, compared with the anticipated circannual variation. The data have been stacked over idealized cycles with a period of either 1.09 (top) or 1.00 (bottom) year. The absence of a yearly pattern and instead the presence of a half-yearly pattern is clearly apparent, more cases being reported in the spring and autumn than in the summer and winter (bottom). This impression is validated by one-way analysis of variance, using two classes anticipating a 6-month component ($P = 0.031$). The fit of a precise yearly component is not statistically significant (see dotted line at bottom). By contrast, the continuous line on top, corresponding to the neartransyear, shows a smooth pattern, further validated by cosinor on the timepoint means ($P = 0.027$). © Halberg.

Fig. 5.

Data from Landau et al. [34] on the incidence of autism and that of mental retardation without features of autism as a function of month of birth. The half-year reaches borderline statistical significance in a multiple component model including a 3-month (autism) or 4-month (mental retardation) component (Autism: $P = 0.092$; MR: $P = 0.080$). There is a large difference in acrophase of the half-yearly component between the two diagnoses, the 90% confidence intervals of the acrophase being non-overlapping (Autism: $\phi = -160^\circ$, 90% CI: -118 to -203 ; MR: $\phi = -28^\circ$, 90% CI: -347 to -69 ; $360^\circ \equiv 0.5$ year, $0^\circ = \text{Jan } 1$). MR: mental retardation. © Halberg.

Fig. 6. Daily incidence of suicide in Minnesota (1968–2002; 35years). Data shown as monthly averages (top left) since daily incidence varied in narrow range of 0–9 (total number of suicides = 15,881). In addition to a long-term trend and a circannual/circasemiannual variation, two transyears with periods of about 1.3 and 1.07 years are detected by least squares spectrum (top right). The circannual waveform is contributed mostly by a 6-month component peaking around the equinoxes (middle left). A prominent weekly variation is also documented peaking on Mondays (middle right). The waveforms of the far-transyear (bottom left) and of the near-transyear (bottom right) are also visualized. © Halberg.

Nonlinear Estimation of about 21-year component in autism compared with live births as a function of time of birth (1947–1979) [27]

Table 1

Series	Period (y)	(95% CI)	Amplitude	(95% CI)	Phase (22.207y)
Clinic	20.17	(16.27 24.07)	21.26	(11.45 31.08)	–328
NAS	22.77	(15.55 29.98)	6.48	(1.02 11.94)	–272
Live Births	23.68	(21.61 25.75)	4.76	(3.93 5.60)	–300

CI: confidence interval; Phase: measure of timing of overall high values recurring in each cycle, expressed in negative degrees, with 360° equated to 22.207 years, and 0° set to 1947, the start of the series.

The average period is 22.207 years, very close to the period of the Hale cycle estimated for the same span (1947–1979) as 22.214 (95% CI: 20.48, 23.95) years by nonlinear least squares. Analyses at a common trial period selected as the best-fitting period of the Hale cycle (22.214 years) yield estimates for the clinic sample, the NAS sample and live births as follows: MESORs of 31.7, 29.0, and 29.6, respectively; amplitude: 20.42, 6.66, and 4.89, respectively; and acrophase: –328, –256, and –302, respectively (by reference to the start of the data series in 1947). By parameter tests, no difference in MESOR is found but differences in amplitude are detected ($P < 0.001$), the clinic sample having an amplitude larger than either the NAS sample or live births, used as control. A small difference in acrophase between the clinic sample and live births ($P = 0.015$) is not seen between the NAS sample and live births ($P > 0.200$).