Influence of light exposure during early life on the age of onset of bipolar disorder

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Abstract

Background: Environmental conditions early in life may imprint the circadian system and influence response to environmental signals later in life. We previously determined that a large springtime increase in solar insolation at the onset location was associated with a younger age of onset of bipolar disorder, especially with a family history of mood disorders. This study investigated whether the hours of daylight at the birth location affected this association.

Methods: Data collected previously at 36 collection sites from 23 countries were available for 3896 patients with bipolar I disorder, born between latitudes of 1.4N and 70.7N, and 1.2S and 41.3S. Hours of daylight variables for the birth location were added to a base model to assess the relation between the age of onset and solar insolation.

Results: More hours of daylight at the birth location during early life was associated with an older age of onset, suggesting reduced vulnerability to the future circadian challenge of the springtime increase in solar insolation at the onset location. Addition of the minimum of the average monthly hours of daylight during the first 3 months of life improved the base model, with a significant positive relationship to age of onset. Coefficients for all other variables remained stable, significant and consistent with the base model.

Conclusions: Light exposure during early life may have important consequences for those who are susceptible to bipolar disorder, especially at latitudes with little natural light in winter. This study indirectly supports the concept that early life exposure to light may affect the long term adaptability to respond to a circadian challenge later in life.

Keywords: bipolar disorder, age of onset, sunlight, insolation, hours of daylight

Introduction

Environmental conditions during early life may amplify individual vulnerability to psychiatric disease later in life, especially in those with a genetic susceptibility to a specific disease (Bale et al., 2010; Gluckman et al., 2008; Rutter, 2005). Multiple studies have reported an association between bipolar disorder and stressful early life events such as gestational hunger (Brown et al., 2000), gestational influenza (Machon et al., 1997; Parboosing et al., 2013), childhood abuse (Daglas et al., 2014; Etain et al., 2008; Gilman et al., 2014) and early parental loss (Morotensen et al., 2003). Early life events that may induce circadian dysfunction are of particular interest since bipolar disorder involves the disruption of many biological rhythms affecting the 24 hour sleep-wake cycle, energy and alertness (Giglio et al., 2009; McClung, 2013; Murray and Harvey, 2010; Wirz-Justice, 2006). The most recognized symptoms of circadian disruption are ongoing sleep disturbances that increase prior to and during episodes (Murray and Harvey, 2010; Ng 2014). However, the consequences of sleep and circadian disruption extend to include irregularity in daily routines, impaired functioning, vulnerability to stressors, and increased risk of episode recurrence (Frank et al., 2000, Giglio et al., 2010; Shen et al., 2008, Sylvia et al., 2009).

At birth, the human circadian system is still immature and developing, and the physical environment may influence its maturation by means of complex epigenetic mechanisms (Azzi et al., 2014; Brooks and Canal, 2013; Ciarleglio et al, 2011; Gluckman et al., 2005; Masri and Sassone-Corsi, 2010; Rivkees, 2007). It was postulated that exposure to light during early life imprints an individual's circadian clock, setting vulnerability to

future environmental challenges to the circadian system (Ciarleglio et al, 2011;Erren et al., 2011). We previously found that the larger the springtime increase in solar insolation at the onset location, the younger the age of onset of bipolar I disorder, especially for those with a family history of mood disorders (Bauer et al., 2012; Bauer et al., 2014). Solar insolation is a measure of the electromagnetic energy from the sun that reaches a surface area on the earth in units of $kWh/m^2/day$ (kilowatt hours/square meters/day) (NASA, 2012). The purpose of the current analysis was to investigate if sunlight present at an individual's birth location would impact the challenge to the circadian system from the springtime increase in solar insolation at the onset location. The developing circadian clock in infants can be entrained, or synchronized to the earth's 24-hour day/night cycle, using cycled lighting of only 200 lux (Rivkees et al., 1997, Rivkees et al., 2004). For comparison, the illumination of bright sunlight is estimated at about 100,000 lux per square meter at the earth's surface (Tiwari and Dubey, 2010). Since low intensity lighting is sufficient for entrainment, the hours of daylight at the birth location were investigated rather than the solar insolation.

Methods

Data collection

All data in this analysis were collected previously to investigate the impact of solar insolation on the age of onset of bipolar disorder (Bauer et al, 2014). Patient data were collected from 36 collection sites in 23 countries: Aarhus, Denmark; Athens, Greece; Bangalore, India; Barcelona, Spain; Beer Sheva, Israel; Buenos Aires, Argentina; Cagliari, Sardinia, Italy; Calgary, Canada; Cape Town, South Africa; Dresden,

Germany; Halifax, Canada; Helsinki, Finland; Hong Kong; Kansas City, KS, USA; Kuala Lumpur, Malaysia; Los Angeles, CA, USA; Medellín, Colombia; Melbourne/Geelong, Australia; Oslo, Norway; Paris, France; Palo Alto, CA, USA; Porto Alegre, Brazil; Rochester, MN, USA; Salvador, Brazil; San Diego, CA, USA; Santiago, Chile; São Paulo, Brazil; Poznan, Poland; Siena, Italy; Thessaloniki, Greece; Tokyo, Japan; Trondheim, Norway; Vitoria-Basque Country, Spain; Wiener Neustadt, Austria; Worcester, MA, USA; and Würzburg, Germany. Data were gathered by direct interviews and reviewing records in 20 sites, primarily by direct interviews in 8 sites, and primarily by reviewing records in 8 sites. Approval was obtained from the ethics committees according to local requirements.

All patients in this study had a diagnosis of bipolar disorder made by a psychiatrist according to DSM-IV criteria. A minimal number of variables were requested to obtain data from locations with a wide range of solar insolation. The variables obtained for each patient were sex, date of birth, age of onset, onset location, birth location, family history of any mood disorder in a first degree relative, and polarity of the first episode (depressed, manic or hypomanic). The age of onset was defined as the first occurrence of an episode of depression, mania or hypomania according to DSM-IV criteria.

Database characteristics

Data were obtained for a total of 5498 patients, slightly larger than that in the previous study (Bauer et al, 2014). Of the 5498 patients, 4054 had a diagnosis of bipolar I disorder, 1252 of bipolar II disorder and 192 of bipolar NOS. The percentage of patients

with a diagnosis of bipolar I disorder at the collection sites varied from 23% to 99%. Since the proportion of bipolar II and bipolar NOS in the dataset were inconsistent across the collection sites, only the 4054 patients with bipolar I disorder were included in the analysis. Of the 4054 patients, 158 were excluded due to missing birth data, leaving 3896 patients with a diagnosis of bipolar I disorder for analysis.

Early Life

Early life was defined as the first 6 months after birth since most circadian systems progressively mature between 1-3 months of age, with cortisol variation appearing between 3-6 months of age (Rivkees 2003, 2007). While the birth month was available for the 3896 patients with bipolar I disorder, the specific day of birth was missing for 429 patients (11%). Considering only the 3467 patients with the day and month of birth available, 1088 were born between days 1-9, 1277 between days 10-20, and 1102 on greater than day 20. The 429 patients without the specific day of birth were included in the analysis without knowing if the day of birth was in the beginning or the end of the month. As a result, the smallest period of time considered was the birth month plus the following month, or two months total. All hours of daylight variables were investigated using the first 2 through 6 months of life.

Sunlight parameters

The average monthly solar insolation values were obtained from the NASA Surface Meteorology and Solar Energy (SSE) database version 6.0 based on data collected over the 22 year period from 1983 to 2005 (NASA, 2012). The solar insolation values

were obtained for the onset locations. The monthly pattern of solar insolation varies by latitude, with little change throughout the year at the equator and large changes at locations close to the north or south poles. However, the solar insolation of locations at the same latitude but different longitude often vary due to local conditions such as cloud cover, altitude, and proximity to large bodies of water. The solar insolation values are available for a 1º x 1º grid of latitude and longitude worldwide, and the onset locations were grouped accordingly. The monthly solar insolation data for the southern hemisphere were shifted by 6 months for comparison to locations in the northern hemisphere. The maximum increase in monthly solar insolation for every onset location was determined.

The SSE database also provides the average monthly hours of daylight. The hours of daylight is the number of hours between sunrise and sunset. The hours of daylight values were obtained for the birth locations. The variables created were the minimum, maximum, average and sum of the average monthly hours of daylight for the birth month and following months.

Approach to analysis

This study analyzed if the hours of daylight parameters at the birth location would impact a base model to assess the relation between the age of onset of bipolar disorder and solar insolation, determined in prior research (Bauer et al., 2014). The base model included the following variables: maximum increase in solar insolation at the onset

location, the interaction of family history and the maximum increase in solar insolation at the onset location, country median age for the onset location, and the birth cohort.

The country median age for the onset location and the birth cohort were included in all models because they are age-related confounders apart from the sunlight effects. At the collection sites, the country median age varied by about 20 years between the oldest (Japan 45.8 years) and youngest (South Africa at 25.5) (CIA World Factbook, 2013). For a disease with an age of onset that spans several decades such as bipolar disorder, an older age of onset would be expected in a country with an older population (Chen et al., 1993; Heimbuch et al., 1980). Previous research has reported a large birth cohort effect in bipolar disorder, with an older onset in older cohorts (Bauer et al., 2015; Chengappa et al., 2003). Three birth cohort groups were created: born before 1940, born between 1940 and 1959, and born after 1959 (Bauer et al., 2014; Chengappa et al., 2003).

Statistics

Generalized estimating equations (GEE) were used to accommodate the correlated data and unbalanced number of patients within the birth locations. A GEE uses a population averaged or marginal approach, estimating the effect across the entire population rather than within the correlated birth locations (Zeger and Liang, 1986). All GEE models have the age of onset as the dependent variable, included the variables in the base model, and some included hours of daylight variables for the birth locations. The quasi-likelihood independence model criterion was used to assess the model fit

(Pan, 2001). A significance level of 0.01 was used to evaluate estimated coefficients, and Sidak's adjustment was used to evaluate multiple comparisons at the 0.01 level. The unadjusted mean age of onset was also determined solely to compare the sample with prior studies that did not adjust for the country median age or birth cohort. All analyses were performed using SPSS Version 22. 0

Results

Although the data for the 3896 patients were collected in 36 cities in 23 countries, there were 398 onset locations, and 485 birth locations for the 3896 patients. The latitude of the birth locations ranged between 1.4 N and 70.7 N, and 1.2 S and 41.3 S. Of the 485 birth locations, 391 were in the northern hemisphere and 94 in the southern hemisphere with the distribution of the birth site latitudes shown in Table 1. Some examples of the most extreme hours of daylight in December and June for the birth locations in this sample are shown in Table 2. Of the 3896 patients, 58.8% were female and family history information was available for 3215 patients (82.5%). The demographic characteristics of the patients are shown in Table 3. The unadjusted mean age of onset for the 3896 patients was 25.4 years.

The most significant daylight variable was the minimum of the average monthly hours of daylight for the birth location for the first 3 months of life. The addition of this variable yields a significant estimated coefficient, enhanced the base GEE model, and did not disturb the prior relationships. The coefficients for all the original variables in the base model, and in the model with the new variable were significant and remarkably stable as

shown in Table 4. The results show that a one hour increase in the minimum of the average monthly hours of daylight in the first 3 months of life is associated with slightly more than a 2 1/2 month increase in the age of onset. The pattern of the association of the minimum of the average monthly hours of daylight during the first 6 months of life is shown in Table 5. Over the time periods investigated, the maximum, average and sum of the average monthly hours of daylight also had some significant coefficients, but these were less significant than the minimum of the average monthly hours of daylight.

Discussion

The current findings indirectly support the hypothesis that early life exposure to light may affect the long-term adaptive responses of the circadian system (Erren et al., 2011; Ciarleglio et al., 2011; Brooks and Canal, 2013). We previously found that the greater the springtime increase in solar insolation at the onset location, the younger the age of onset of bipolar disorder, especially for those with a family history of mood disorders. This analysis has extended our understanding to include a positive relationship between the lowest average monthly hours of daylight hours at the birth location in the first 3 months of life and the age of onset, such that more daylight lessens vulnerability to the future circadian challenge of the springtime increase in solar insolation at the onset location.

Diverse lines of evidence support the concept that early life environmental light may have long-term impact on the circadian system, although research in this area remains limited and primarily on animals. First, unlike many mammals, primates can respond to

light at an early developmental stage (Rivkees, 2007; Watanabe et al., 2013). The first photoreceptors to function are retinal ganglion cells containing melanopsin, which are specialized to detect environmental light and regulate non-visual responses such as circadian synchronization and the pupillary light response (Sekaran et al., 2005; Watanabe et al., 2013). The circadian system of preterm baboons is sensitive to light at an equivalent to 26 weeks gestational age in humans (Hao and Rivkees, 1999). A pupillary light response was detected in preterm human infants at 30-35 weeks gestational age (Robinson and Fielder, 1990; Watanabe et al., 2013), whereas rods start functioning at 34-36 weeks gestational age, and cones about 1 month after birth (Watanabe et al., 2013; Westall et al., 1999). Second, human preterm infants were able to entrain the circadian clock by exposure to low-intensity cycled lighting (Rivkees, 2003; Rivkees et al., 2004). When comparing term and preterm infant circadian entrainment, the length of exposure to a cyclical light-dark environment was more important than neurologic maturity (McMillen et al., 1991). Third, the timing of the association found in this study, over the first 3 months of life, is consistent with prior reports of the progressive development of the circadian system in humans. Between 1-3 months of age, the circadian system gradually matures and organizes physiological and behavioral activity in a 24-hour cycle, including rest/activity, temperature, and hormone secretion (Glotzbach et al., 1994; McGraw et al., 1999; Rivkees, 2007; Shimada et al.,1999). Fourth, mammals raised under varying photoperiods (short versus long days) during the postnatal period exhibit changes to the circadian system that are persistent and associated with future circadian adaptation, animal behavior, retinal function and the immune response (Brooks et al., 2014; Canal et al., 2009;

Ciarleglio et al., 2011; Jackson et al., 2014; Pyter and Nelson, 2006; Smith and Canal, 2009; Weil et al., 2006). For example, newborn mice raised in summer light conditions of long photoperiods had consistent physiologic and behavioral changes to future seasonal light-dark changes, whereas mice raised in winter light conditions of short photoperiods had unstable reactions to future seasonal light-dark changes (Ciarleglio et al., 2011). Other studies in mice found that perinatal light exposure may primarily target long-term adaptive responses of the circadian clock to environmental light (Brooks et al., 2014).

Light available in the first 3 months of life may have important long-term consequences for those at risk for bipolar disorder, especially at latitudes where little sunlight would enter an infant's room in winter months. However, this analysis cannot determine threshold values for too little or too much sunlight in early life, and too much or constant light exposure in early life may also disrupt the developing circadian clock (Mann et al., 1986; Ohta et al., 2006). The time of day of light exposure may also impact circadian development (Harrison, 2004; Rivkees 2003). Cyclic light-dark cycles are recommended for lighting in early life (Miller et al., 1995; Rivkees et al., 2004; Watanabe et al., 2013), and research is ongoing to determine optimal indoor lighting for non-visual functions across the lifespan (DIN, 2011; IES, 2008; Lucas et al., 2014). Lighting for circadian vision is quite complex since the spectral sensitivity of melanopsin is for a shorter wavelength (blue light) than of photoreceptors in rods and cones involved in visual performance, and since the physiological need for light to stimulate circadian vision varies greatly over a 24 hour period and with age (Lucas et al., 2014).

Sunlight also suggests a role for vitamin D, but the serum levels or use of vitamin D supplementation during the gestational and perinatal periods were not known. In animal studies, vitamin D is involved in brain development (Eyles et al., 2013), and in humans, low Vitamin D in early life is associated with an increased risk for psychiatric disorders including schizophrenia (Allen et al., 2013; McGrath et al., 2010; McGrath et al., 2004;).

There are other limitations to this study. The process of diagnostic assessment was not standardized across the collection sites, although based on DSM-IV criteria. There may be recall bias in the age of onset that was self-reported by patients. There may be ascertainment bias since patients with bipolar disorder may recognize symptoms in offspring, resulting in earlier diagnosis. Family history data is often unreliable (Hardt and Franke, 2007) and reflects cultural bias (Karasz, 2005), but has been used successfully in other studies (Baldessarini et al., 2012; Romero et al., 2007). However, the unadjusted age of onset of 25.4 years in this study is similar to that found in prior international studies, with a mean of 25.7 years for 1665 patients with bipolar I disorder (Baldessarini et al., 2012), and 25.6 years for 1041 patients with bipolar disorder (Morselli et al., 2003). There was no way to determine the actual exposure to light during early life. This analysis also does not address what type of lighting or light exposure will improve infant circadian entrainment, or whether early life light exposure impacts the response to other circadian challenges such as shift work, light pollution, social jet lag or travel across time zones (Chepesiuk, 2009; Fountoulakis, 2010; Wittmann et al., 2006). Other factors that may influence the age of onset of bipolar disorder such as drug abuse (González-Pinto et al., 2008), medical history or course of

illness were not included. This study does address the diverse cultural and social aspects of seasonality, and shifted the data from the southern hemisphere for analysis. Finally, these models show an association but cannot show causality.

This preliminary study raises many questions about the long term effects of early life light exposure on later life challenges to the circadian system in patients with bipolar disorder. In addition to a younger onset, reduced early life light exposure may lead to negative consequences in the course of the illness such as sleep disturbances or rapid cycling. It may also influence sensitivity to treatments that act directly on circadian systems such as light therapy, sleep deprivation or melatonergeric agonists. There may be a connection between early life light exposure and circadian gene polymorphisms. Early life light exposure may be associated with variables that can be measured before the first episode such as chronotype. The optimal lighting in early life for those with a family history of bipolar disorder should be investigated, including spectral composition, timing and intensity. Further research is needed into the impact of sunlight on the onset and course of bipolar disorder.

Conflict of Interest:

The authors declare that they have no conflicts of interest.

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Table 1. Distribution of birth sites by latitude group (N=3896)

Latitude Group (Degrees)*	N Sites	% Sites
0 to 9	38	7.8
10 to 19	42	8.7
20 to 29	56	11.6
30 to 39	120	24.7
40 to 49	161	33.2
50 to 59	49	10.1
60 to 69	17	3.5
70 to 80	2	0.4
Total	485	100.0

* Includes 391 northern hemisphere birth sites with 2848 patients and 94 southern hemisphere birth sites with 1048 patients.

Table 2. Selected extreme minimum monthly hours of daylight for birth locations in December and June*

Birth location	Latitude (Degrees N/S)	Minimum monthly daylight hours in December	Minimum monthly daylight hours in June
Hammerfest, Norway	70.67 N	0.0	24.0
Reykjavik, Iceland	64.16 N	4.5	20.8
Helsinki, Finland	60.20 N	6.0	18.7
Oslo, Norway	59.92 N	6.1	18.6
Aarhus, Denmark	56.20 N	7.1	17.5
Edmonton, Canada	53.55 N	7.6	16.7
Poznan, Poland	52.40 N	7.8	16.7
Kannur, India	11.90 N	11.4	12.8
Panama City, Panama	8.96 N	11.6	12.6
Medellin, Columbia	6.30 N	11.7	12.4
Kuala Lumpur, Malaysia	3.20 N	11.9	12.3
Belem, Brazil	1.45 S	12.0	12.2

* Southern hemisphere data converted from June to December and December to June.

Table 3. Demographics of patients with bipolar I disorder

Data Category	All Bipolar I Patients (N=3896) N	%	Bipolar I Patients with Family History Data (N=3215) N	%
Gender				
Female	2290	58.8%	1884	58.6%
Male	1606	41.2%	1331	41.4%
Birth Cohort				
Born Before 1940	208	5.3%	181	5.6%
Born Between 1940 and 1959	1213	31.1%	1000	31.1%
Born After 1959	2475	63.5%	2034	63.3%
Family History				
Yes	1763	45.3%	1763	54.8%
No	1452	37.3%	1452	45.2%
Missing	681	17.5%		

Table 4. Comparison of estimated GEE models, with and without the minimum of the average monthly hours of daylight at the birth location for the first 3 months of life

	Base model*			Base model with minimum daylight hours*		
	Coefficient	SE	P**	Coefficient	SE	P**
Constant	20.327	2.634	<0.001	17.461	2.793	<0.001
Onset location country median age	0.173	0.057	0.003	0.170	0.058	0.002
Onset location maximum increase in monthly insolation	-4.476	1.145	<0.001	-4.348	1.126	<0.001
The interaction between family history and onset location maximum increase in monthly insolation (No)	2.250	0.314	<0.001	2.269	0.315	<0.001
The interaction between family history and onset location maximum increase in monthly insolation (Yes)	0***			0***		
Birth cohort (<1940)	15.531	1.781	<0.001	15.546	1.785	<0.001
Birth cohort (1940-1959)	7.147	0.571	<0.001	7.183	0.576	<0.001
Birth cohort (>1959)	0***			0***		
Minimum average monthly hours of daylight for first 3 months at birth location				0.221	0.073	0.003

* N=3215, Clusters=395.
** Wald chi-square hypothesis test significance level.
*** Parameter is redundant. Set to 0.

Table 5. Comparison of estimated GEE models* for months using the minimum of the average monthly hours of daylight at the birth location

Number of months	Minimum hours of daylight coefficient	SE	P**
2 Months (birth month + 1)	0.190	0.064	0.003
3 Months (birth month + 2)***	0.221	0.073	0.003
4 Months (birth month + 3)	0.264	0.094	0.005
5 Months (birth month + 4)	0.315	0.126	0.012
6 Months (birth month + 5)	0.355	0.174	0.042

* GEE model estimates age of onset with a constant, onset location country median age, onset location maximum increase in monthly insolation, family history x onset location maximum increase in monthly insolation, birth cohort and the minimum of the average number of daylight hours for the first 2 to 6 months of life at birth location. N=3215, clusters=395.
** Wald chi-square hypothesis test significance level.
***Best fitting model with the lowest quasi-likelihood independence model criterion.