Circadian timing system (CTS) characteristics in bipolar disorder: investigation of possible endophenotypes

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Manic and bipolar mood disorders and disturbances
Study type	Observational invasive

Summary

ID

NL-OMON39203

Source
ToetsingOnline

Brief title
Circadian rhythms in bipolar disorder

Condition

- Manic and bipolar mood disorders and disturbances

Synonym
bipolar disorder, manic depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: National Institute of Mental Health (NIMH;USA)

Intervention

Keyword: Actigraphy, Bipolar Disorder, Circadian rhythm, Endophenotype

Outcome measures

Primary outcome

Identifying circadian parameters as possible endophenotypes for bipolar disorder. The circadian parameters assessed in this study include rest-activity rhythm parameters (total sleep duration, sleep onset latency, sleep efficiency, interdaily stability and intradaily variability), chronotype and circadian rhythm of gene expression.

Secondary outcome

- Effects of moodstabilizers and other medication on circadian rhythm parameters.

- Relationship between mood state at study entry and circadian rest-activity rhythms.

Study description

Background summary

Bipolar disorder (BD), also known as manic-depressive illness, is a brain disorder that causes unusual shifts in a person*s mood, energy, and ability to function. BD typically develops in late adolescence or early adulthood and is present in roughly two percent of the population aged 18 and older in any given year. BP is highly heritable, based on the results of several twin studies. First-degree relatives of BP probands have a 20-fold increased risk for BD compared with relatives of healthy individuals. Adoption studies show that increased familial
aggregation is not simply due to environmental factors. Despite the fact that

increased risk for BP inherited, the disorder's genetic basis remains elusive.

Importance of endophenotypes
Due to the genetic heterogeneity, it is hard to successfully link genetic loci to bipolar disorder. Therefore it is important to, in addition to GWA studies, also consider other approaches to investigate the etiology of bipolar disorder. One of these approaches is to make use of traits that often accompany bipolar disorder, known as endophenotypes. Biological endophenotypes are measurable intermediate phenotypes that are generally closer to the action of the gene and thus exhibit higher genetic signal-to-noise ratios. Endophenotypes involved in BD might be abnormal neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological findings.

Endophenotypes in BD
Despite the overlap and comparable prevalence and public health importance between BD and schizophrenia there has been less study of possible endophenotypes for BD than for schizophrenia. Traits of interest for the use as endophenotypes in BD are abnormal regulation of circadian rhythms, response to sleep deprivation, P300 ERP*s, response to medication and increase in white matter hyperintensities.

Rhythms and activity as endophenotypes of BD
For this study we will focus on the regulation of circadian rhythms and activity, as altered circadian and infradian rhythmicity is a key aspect of recurrent mood disorders and has been proposed as a possible endophenotype. Euthymic BD twins show greater seasonal changes in sleep length and mood and higher global seasonality-scores than unaffected co-twins. Family and twin studies point to genetic components in seasonal affective disorder and seasonality (seasonal variations in mood and behavior) and there is moderate-high heritability for diurnal preference, sleep length and sleep quality. Bipolar patients show less stable and more variable activity patterns then controls and variability of the rest-activity rhythm alone is a significant independent predictor of diagnostic group.

Study of cultured fibroblasts
Fibroblast cell cultures can be relatively easily obtained from small skin biopsies. As they originate from the same embryonic layer as neurons they provide a valuable paradigm for cellular research of neuropsychiatric disorders. Several studies have shown that circadian oscillators in fibroblasts are similar to those operative in the brain. Fibroblasts are therefore a valid in vitro model for molecular oscillators in the brain. Similar to the circadian pacemaker in the mammalian brain, cultured cells, including fibroblasts, harbor self sustained and cell-autonomous circadian clocks that persist even during cell division. The periods for the circadian gene expression in fibroblasts have been found to correspond closely with the human circadian physiology and mouse behavior. Altered rhythmic expression patterns have been found in cultured fibroblasts of bipolar patients in several clock

genes.

Summary
BD is a complex psychiatric trait with unknown susceptibility factors. It is important to investigate possible endophenotypes for bipolar disorder, like deviations in circadian rhythmicity in vivo by using actimetry as well as in vitro, using fibroblast cell cultures.

Study objective

The objective of this study is to include 200 cases, 200 unaffected first and second degree family members and 200 unrelated healthy controls to participate in the assessment of variability in activity and light exposure, as these domains are critical features of the neurobiological underpinnings of BD. Based on prior evidence for heritability of several of these features (Freimer, unpublished), we expect that they will be important in the Quantitative Trait Locus (QTL) analyses.

Study design

For this study we will recruit 200 cases, 200 unaffected first and second degree family members and 200 unrelated healthy controls to collect circadian rest-activity measurements for comparison. These subjects will be part of the same homogeneous Dutch population that have earlier participated in the study *the genetics of bipolar disorder* (CCMO nr NL62946.041.10). Data collection is completed in year 4.

The timeline of the proposed 5-year project is provided in table below. Four years are needed to complete recruitment and sample collection of 3 groups of 200 participants. Statistical analyses are initiated in the fourth year and continue in year 5. Data will be released to the scientific community starting at the end of year 4 until the end of the proposed project.

For this study we will use the following data from the *Genes of bipolar disorder* study (protocol 10-285): demographic data, genetic information from the GWAS. For this study five additional questionnaires will be used; the current mood state will be assessed with the ASRM and IDS, the Seasonal Pattern Assessment Questionnaire (SPAQ), the Munich Chronotype Questionnaire (MCTQ), a questionnaire on physical activity (IPAQ), and a questionnaire on current use of medication. Also, waist circumference will be measured. Supplemented with Actimetry, using the Actiwatch-2, this is a reliable and well-validated approach to collect activity data.

Fibroblast cell lines
The fibroblast cell lines are obtained by a skin biopsy at the upper arm using

a 3 mm punch (Stiefel). Circadian rhythm will be assed in cell lines with genetic variants of interest using standard target RNA expression profiling (qPCR of selected transcripts using TaqMan technology) at regular 2 hours intervals for 48 hours.

Study burden and risks

Wearing the Actiwatch has no risks for the participant. The only potential burden is that participants have to wear the watch on their wrist for two weeks. Future benefits may include development of better treatment of symptoms or even prevention of developing BD. As the project involves minimal risk to participants and the potential benefits in terms of knowledge gained are quite large, the benefits clearly outweigh the risks.
Risk of skin biopsy is neglectable and consists of minor risk for infection or scar tissue. To minimize this, biopsies will be taken by qualified medical personal in dedicated medical clinic rooms. To limit cosmetic disadvantages biopsies will be taken at places indicated by the participants (generally behind the elbow).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Patients:
- Bipolar I disorder according to the DSM-IV , with medical record of at least one clinical treatment for mania
-Dutch ancestry
-Age >18 years;Healthy controls:
-Age>18 years
-Dutch ancestry
-IQ >80 ;Family member:
- no bipolar I disorder.

Exclusion criteria

Patients:
-Age <18 years
-Premorbid IQ <80
-Poor physical health or suffering from severe dementia or other neurodegenerative disease
-Patients under current treatment or detention under the Dutch governmental health act
-Use of anti-coagulants
-Pregnancy;Family members:
-Bipolar I disorder
-Age <18 years
-IQ <80
-Poor physical health or suffering from severe dementia or other neurodegenerative disease
-Use of anti-coagulants
-Pregnancy
Healthy controls:
- Age < 18 years
- IQ < 80
-Use of anti-coagulants
-Poor physical health or suffering from severe dementia or other neurodegenerative disease
-Pregnancy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-04-2013
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO Date:	18-10-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL36370.041.11