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TESE DE DOUTORADO

DANIEL GOMES COIMBRA

SAZONALIDADE DO COMPORTAMENTO SUICIDA:
EVIDÊNCIAS DO PAPEL DA LUZ COMO UM POSSÍVEL MODULADOR

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EVIDÊNCIAS DO PAPEL DA LUZ COMO UM POSSÍVEL MODULADOR

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências da Saúde, do Instituto de Ciências Biológicas e da Saúde da Universidade Federal de Alagoas, como parte dos requisitos para obtenção do título de Doutor em Ciências da Saúde.

Orientador: Prof. Dr. Tiago Gomes de Andrade

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Sazonalidade do comportamento suicida: evidências do papel da luz como um possível modulador.

Tese submetida ao corpo docente do Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Alagoas e aprovada em 27 de setembro de 2018.

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"To every thing there is a season, and a time to every purpose under the heaven"
Eclesiastes 3:1

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APRESENTAÇÃO DA TESE

A tese está estruturada em formato de artigos científicos, contemplando os seguintes manuscritos:

PRIMEIRO ARTIGO

Título: *Do suicide attempts occur more frequently in the spring too? A systematic review and rhythmic analysis*. Artigo publicado na *Journal of Affective Disorders* 196 (2016) 125–137.

SEGUNDO ARTIGO

Título: *Seasonal Variation of Suicides in Brazil: Evidences for a Latitude Effec*t.

TERCEIRO ARTIGO

Título: *Increased photoperiod induces an antidepressant-like behavior and disrupted rhythmic expression of mPer2 and mBdnf in brain regions associated with suicide*.

RESUMO

O suicídio é um grave problema de saúde pública em todo o mundo. A cada ano, aproximadamente 800.000 pessoas cometem suicídio e estima-se que para cada suicídio cometido, deve haver outras 20 tentativas. Foram relatadas diferenças entre indivíduos que tentaram suicídio e aqueles que consumaram o suicídio. Estes que consumaram tendem a ser do sexo masculino, mais velhos, menos impulsivos, usando métodos mais letais, deixam nota de suicídio e são mais deprimidos. Aqueles que tentam e não efetivam o suicídio, tendem a ser do sexo feminino e utilizam método não-violento, como o envenenamento. Apesar dessas diferenças, um padrão sazonal tem sido descrito com pico na primavera/verão, mas há divergências nas tentativas de suicídio. Esta ausência de consenso nos permitiu avaliar através de uma revisão sistemática, se essas tentativas ocorrem com maior frequência na primavera/verão assim como já descrito para os casos de suicídio. Um perfil sazonal semelhante às ocorrências de suicídio foi encontrado também para tentativas de suicídio. Este comportamento sazonal sugere a influência de um modulador ambiental, e como a luz é o principal agente sincronizador do ritmo endógeno com o ambiente através do ciclo claro-escuro, é provável que também seja um importante agente dos ritmos circanuais/sazonais. Como o Brasil é um país com grande extensão territorial, atravessando a linha do Equador (latitude 0º) e o Trópico de Capricórnio (latitude S24°14’), investigamos a influência da latitude e fotoperíodo na sazonalidade dos suicídios em todas as cidades brasileiras no período de 2010 a 2015. A variação sazonal dos suicídios teve pico no final da primavera/início do verão e nadir no inverno. Este perfil sazonal é melhor observado à medida que decresce a latitude. Quanto mais distante da latitude 0º, maiores as taxas de suicídio e amplitude (razão pico/vale), além de correlação em fase entre a sazonalidade das ocorrências de suicídio e o fotoperíodo. Assim como várias doenças têm sido associadas a perturbações no ritmo circadiano, esta modulação ambiental do ritmo circadiano pode ter papel relevante na formação do comportamento suicida sazonal em indivíduos com vulnerabilidade. Em animais, a manipulação do fotoperíodo, simulando estações do ano, resulta em alterações no perfil de expressão gênica e comportamental. Estudamos em camundongos C57BL/6J, o efeito da variação gradual do fotoperíodo, simulando do inverno ao verão em curto tempo, para observar o efeito molecular em estruturas cerebrais relacionadas ao suicídio em humanos e alterações comportamentais. Uma redução importante e perda de ritmicidade em genes circadianos foi encontrada, além de um efeito tipo antidepressivo no teste do nado forçado. A influência fotoperiódica observada em modelos animais associada a relatos de sazonalidade do suicídio apenas em países distantes da latitude 0º, onde há alterações significativas no fotoperíodo, reforçam a participação da luz como um importante modulador da sazonalidade do comportamento suicida.

PALAVRAS-CHAVE: Sazonal, Suicídio, *Per2*, *Bdnf*, Antidepressivo, Nado Forçado, Brasil, Latitude.

ABSTRACT

Suicide is a serious public health problem around the world. Each year, approximately 800.000 people complete suicide and it is estimated that for each suicide committed, there must be another 20 attempts. Differences have been reported between individuals who attempted suicide and those who committed suicide. These tend to be male, older, less impulsive, using more lethal methods, leave suicidal note and are more depressed. The attempters tend to be female and use a non-violent method, such as poisoning. Despite these differences, a seasonal pattern has been described with peak in the spring / summer, but there are divergences in suicide attempts. This lack of consensus allowed us to evaluate through a systematic review if these attempts occur more frequently in the spring / summer as already described for cases of suicide. A seasonal profile similar to the occurrences of suicide was also found for suicide attempts. This seasonal behavior suggests the influence of an environmental modulator, and since light is the main synchronizing agent of the endogenous rhythm with the environment through the light-dark cycle, it is also likely to be an important agent of the circannual / seasonal rhythms. As Brazil is a country with great territorial extension, crossing the Equator line (latitude 0º) and the Tropic of Capricorn (latitude S24°14'), we investigated the influence of latitude and photoperiod in the seasonality of suicides in all Brazilian cities in the period from 2010 to 2015. A seasonal variation of suicides were find with peak in late spring / early summer and nadir in winter. This seasonal profile is better observed as latitude decreases. The further away from latitude 0 °, the higher the suicide rate and amplitude (Peak / Trough ratio), and the in-phase correlation between the seasonality of suicide occurrences and the photoperiod. As several diseases have been associated with disturbances in circadian rhythm, this environmental modulation of the circadian rhythm may play a relevant role in the formation of seasonal suicidal behavior in individuals with vulnerability. In animals, the manipulation of the photoperiod, simulating seasons, results in changes in the gene expression and behavioral profile. We studied, in C57BL / 6J mice, the effect of the photoperiod gradual variation, a simulation from winter to summer, to observe the molecular effect in brain structures related to human suicide and behavioral changes. A significant decrease in circadian gene expression and loss of rhythmicity were found, in addition to an antidepressant-like behavior in the forced swimming test. The photoperiodic influence observed in animal models associated with seasonal suicide reports only in countries distant from 0º latitude, where there are significant alterations in the photoperiod, reinforce the participation of light as an important modulator of the seasonality of suicidal behavior.

KEY WORDS: Seasonality, Suicide, *Per2*, *Bdnf*, Antidepressant-like, Forced Swim test, Brazil, Latitude.

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LISTA DE ABREVIATURAS E SIGLAS

Alpha Activity duration
BD Transtorno Bipolar
BDNF *Brain derived neurotrophic factor*
BMAL1 gene *brain muscle aryl nuclear translocase like-1*
CENTRAL Cochrane Central Register of Controlled Trials
CLOCK *circadian locomoter output cycles protein kaput*
CRY gene da família *Criptocrome*
CT Cycle Threshold
CV Coefficient of variation
EPM Elevated plus maze
FST Forced swimming test
ICD-10 International Classification of Diaseases - 10
ISI Web of Science
L5 5h of lower activity
LD Light-Dark cycle
LD16:8 Long photoperiod
LD8:16 Short photoperiod
LILACS Literatura LatinoAmericana e do Caribe em Ciências da Saúde
M10 The 10 most active hours
Medline Medical Analysis and Retrieval System Online
mPFC medial prefrontal córtex
OFT Open field test
OMS ou **WHO** Organização Mundial de Saúde
P/T Peak-to-Trough ratio
Per gene da família *Period*
RA Relative Amplitude
rAMP relative amplitude value pelo Metacycle
RRE Elementos de Resposta REV
SAD Transtorno Afetivo Sazonal
SCN Núcleo Supraquiasmático
SLA Spontaneous locomotor activity
TSL Transition Short to Long photoperiod protocol
TST Tail suspension test
TTFL Ciclo de retroalimentação transcricional-traducional
ZT Zeitgeber Time

SUMÁRIO

INTRODUÇÃO

O suicídio é considerado um grave problema de saúde pública. Segundo a Organização Mundial de Saúde (OMS), a cada ano, aproximadamente 800.000 pessoas cometem suicídio, sendo uma morte a cada 40 segundos (ORGANIZAÇÃO MUNDIAL DE SAÚDE, 2014). Estima-se que para cada suicídio cometido, deve haver mais 20 outras tentativas. Cada suicídio traz grande impacto para a família, comunidade e para o país, trazendo efeitos nocivos duradouros nas pessoas deixadas para trás.

Em 2016, o suicídio foi considerado a segunda principal causa de morte entre jovens de 15-29 anos e a 18ª causa de morte em todo o mundo. É considerado um fenômeno global, sendo que 79% dos casos ocorrem em países de baixa e média renda, onde os recursos e serviços, quando existem, são frequentemente escassos e limitados para identificação, tratamento e apoio precoces de pessoas necessitadas (ORGANIZAÇÃO MUNDIAL DE SAÚDE, 31 de janeiro de 2018).

Vários fatores de risco têm sido associados ao suicídio. Fatores sociais, psicológicos e culturais podem interagir para levar uma pessoa ao comportamento suicida. O próprio acesso a instrumentos para tentar suicídio e tentativas anteriores são importantes fatores de risco. Embora a relação entre suicídio e transtornos mentais (depressão, alcoolismo, transtorno bipolar) seja bem estreita, muitas tentativas de suicídio acontecem impulsivamente, em momentos de crise, como guerras e desastres, ou uma quebra na capacidade de lidar com os estresses da vida, problemas, relacionamentos conflituosos, discriminação, abuso, violência, crise econômica e desemprego, dor e doença crônica (ORGANIZAÇÃO MUNDIAL DE SAÚDE, 31 de janeiro de 2018).

Segundo Botega (2015), o comportamento suicida é compreendido como todo ato pelo qual um indivíduo causa lesão a si mesmo, independente do grau de intenção letal e do verdadeiro motivo deste ato. Vai desde a ideação (pensamentos de autodestruição), a verbalização da intenção, até a tentativa e a consumação final do suicídio.

Apesar de partilharem a característica principal que é a decisão em tirar a própria vida, alguns estudos descrevem diferenças entre indivíduos que cometeram suicídio e aqueles que tentaram suicídio (DEJONG; OVERHOLSER; STOCKMEIER, 2010; FUSHIMI; SUGAWARA; SAITO, 2006; GINER *et al.*, 2013; MALONE *et al.*, 2007; PARRA URIBE *et al.*, 2013; YOUNES *et al.*, 2015). Os indivíduos que consumaram suicídio eram mais propensos a ser do sexo masculino, mais velhos, menos impulsivos, usaram métodos mais letais, deixavam uma nota de suicídio e tendiam a ficar mais deprimidos do que aqueles com tentativas (baixa possibilidade de letalidade).

Indivíduos que tentam suicídio utilizavam predominantemente o autoenvenenamento, enquanto os suicidas tendiam a executar o enforcamento e usar drogas ou armas de fogo. Apesar da proporção de suicídios concluídos ser duas vezes mais elevada nos homens do que nas mulheres, a taxa de tentativas é mais prevalente nas mulheres, particularmente nas jovens (HAWTON *et al.*, 1998; IRIBARREN *et al.*, 2000; PARRA URIBE *et al.*, 2013; YOUNES *et al.*, 2015).

A OMS reconhece o suicídio como prioridade de saúde pública. Isto pode ser constatado por meio de publicações como o primeiro relatório mundial sobre suicídio, "Prevenção do suicídio: um imperativo global", publicado em 2014, aumentando a conscientização e importância sobre o tema, além de incentivar estratégias de prevenção (ORGANIZAÇÃO MUNDIAL DE SAÚDE, 2014). No Plano de Ação da OMS para a Saúde Mental 2013-2020, os Estados-Membros da OMS comprometem-se a trabalhar para atingir o objetivo global de reduzir a taxa de suicídio nos países em 10% até 2020.

Apesar de muitos fatores contribuírem para o comportamento suicida, um padrão sazonal (ritmo que é sincronizado pelas estações do ano) tem sido descrito em vários estudos (AJDACIC-GROSS *et al.*, 2010; BRIDGES; YIP; YANG, 2005; RÄSÄNEN *et al.*, 2002; WOO; OKUSAGA; POSTOLACHE, 2012) com maior frequência de suicídio na primavera / verão (CAVANAGH *et al.*, 2016; CHRISTODOULOU *et al.*, 2012; PARTONEN *et al.*, 2004; PETRIDOU *et al.*, 2002; ROCCHI *et al.*, 2007) às vezes com diferenças entre sexo (LESTER; FRANK, 1988; YIP; CHAO; CHIU, 2000).

Este padrão sazonal não existe apenas em indivíduos que cometeram suicídio. Um padrão semelhante também foi relatado em tentativas de suicídio (YIP; YANG, 2004), entretanto há divergências quanto à estação de maior frequência (BARKER *et al.*, 1994; JESSEN *et al.*, 1999; MASTERTON, 1991). Esta ausência de consenso na literatura sobre a sazonalidade das tentativas de suicídio nos permitiu avaliar se essas tentativas ocorrem com maior frequência na primavera/verão, assim como já descrito para os casos de óbito por suicídio.

Uma possível explicação para esta variação sazonal nas ocorrências de suicídio é a modulação do sistema circadiano (LEGATES; FERNANDEZ; HATTAR, 2014). Em mamíferos, o ritmo circadiano (*circa* = cerca, *dian* = dia) compreende um sistema multinível integrado de osciladores, capaz de sustentar um período de aproximadamente 24 horas, determinando características fisiológicas a comportamentais. Este sistema temporizador circadiano possui osciladores periféricos que estão subordinados a uma estrutura cerebral chamada núcleo supraquiasmático (SCN), localizado no hipotálamo anterior, e é considerado o "marcapasso central" da ritmicidade circadiana. O SCN pode ser dividido em duas sub-regiões: o *Core* e o *Shell*. Estas estruturas possuem atividades, conectividade retinal e eferente diferenciadas, além de expressão de vários neuropeptídios, como o peptídeo intestinal vasoativo (VIP) e o peptídeo liberador de gastrina (GRP) no *Core*, e células expressando arginina-vasopressina (AVP) no *Shell* (HASTINGS; MAYWOOD; BRANCACCIO, 2018). Entretanto, para que este sistema temporizador interno funcione de forma efetiva, é necessário sincronizar-se com a principal pista ambiental do ciclo claro-escuro, a luz solar. Portanto, a principal função do SCN é de sincronizar múltiplos ritmos endógenos à ritmicidade ambiental através do estímulo luminoso (HASTINGS; MAYWOOD; BRANCACCIO, 2018) (Figura 1A).

Na retina, células ganglionares especializadas contendo o fotopigmento melanopsina tem a função de detectar a luz ambiental. O SCN recebe inervação retiniana direta via trato retino-hipotalâmico (RHT) para sua sincronização aos ciclos claro-escuro. O SCN projeta-se para vários centros cerebrais, muitos dos quais contêm ritmicidade circadiana local, que direcionam o comportamento (por exemplo, alimentação-jejum e sono-vigília), ritmos circadianos autonômicos e neuroendócrinos. Essas pistas sistêmicas sincronizam os relógios moleculares locais dos tecidos periféricos, e esses relógios locais por sua vez direcionam programas locais de expressão gênica circadiana que regulam ritmos fisiológicos essenciais à saúde (por exemplo, ritmos relacionados à agilidade mental, pressão arterial, metabolismo de triglicérides e função renal) (HASTINGS; MAYWOOD; BRANCACCIO, 2018).

No nível molecular, o mecanismo deste sistema temporizador circadiano é composto por ciclos de retroalimentação transcricional-traducional (TTFL), no qual complexos heterodiméricos de *circadian locomoter output cycles protein kaput* (CLOCK) e proteínas cerebrais e musculares tipo ARNT1 (BMAL1) atuam via *Enhancer box* (E-box) que são sequências reguladoras para conduzir a expressão diurna da família *Period* (PER) e proteínas criptocromo (CRY) (Figura 1B). Os complexos PER-CRY se acumulam no núcleo e começam a reprimir sua própria expressão ao suprimir a atividade de CLOCK-BMAL1. Os níveis de RNAm de *Per* e *Cry* caem e os complexos PER-CRY existentes são degradados. A degradação subsequente de PER-CRY na noite circadiana permite que o ciclo comece novamente (HASTINGS; MAYWOOD; BRANCACCIO, 2018).

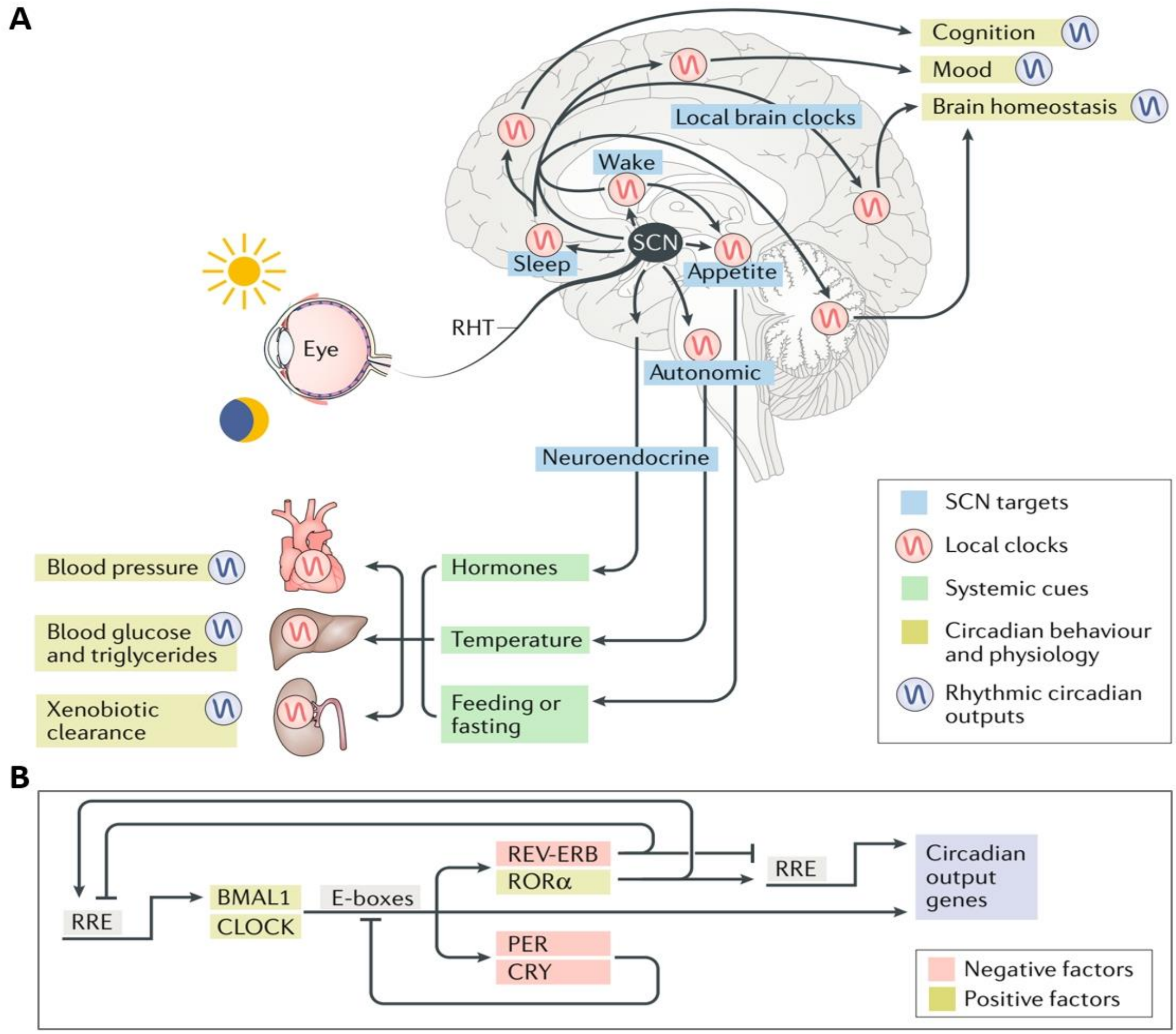

Figura 1. Organização circadiana em mamíferos. **A**- O "marcapasso" central do sistema circadiano é o núcleo supraquiasmático (SCN), localizado no hipotálamo anterior. O SCN recebe inervação retiniana direta via trato retino-hipotalâmico (RHT) e projeta-se para vários centros cerebrais os quais direcionam comportamento, ritmos circadianos autonômicos e neuroendócrinos. Essas pistas sistêmicas terão influência em tecidos periféricos, regulando ritmos fisiológicos essenciais à saúde. **B**- Esquema simplificado dos ciclos de retroalimentação transcricional-tranducional (TTFL) moleculares do relógio circadiano de mamíferos. As proteínas CLOCK e BMAL1 formam heterodímeros e atuam via E-box para conduzir a expressão diurna PER e CRY. Estes também se heterodimerizam para suprimir a atividade de CLOCK-BMAL1. A degradação PER-CRY permite que o ciclo comece novamente. Outras alças de retroalimentação incluindo receptores nucleares (REV-ERB e RORα) também são regulados pelo circuito circadiano via E-box e controlam a expressão de BMAL1 via elementos de resposta REV (RREs). Por sua vez, esses circuitos principais e auxiliares acionam programas circadianos locais de genes de saída controlados pelo relógio (*clock-controlled genes*), que também são regulados por CLOCK–BMAL1, PER–CRY e REV-ERB e RORα via E-boxes e RREs. Fonte: Adaptado de Hastings, Maywood and Brancaccio, 2018.

Ciclos de realimentação adicionais incorporando receptores nucleares (REV-ERB e RORα) também são regulados pelo circuito circadiano via E-box e controlam a expressão de BMAL1 via elementos de resposta REV (RREs) (Figura 1B). Isso estabiliza e aprimora o núcleo da TTFL. Por sua vez, esses circuitos principais e auxiliares acionam programas circadianos locais de genes de saída controlados pelo relógio (*clock-controlled genes*), cujos primeiros níveis também são regulados por CLOCK–BMAL1, PER–CRY e REV-ERB e RORα via E-boxes e RREs (HASTINGS; MAYWOOD; BRANCACCIO, 2018).

Estudo recente de Fernandez *et al.* (2018) mostrou que não apenas o SCN tem papel importante na sincronização endógena com o ambiente, mas também uma estrutura chamada núcleo perihabenular (PHb) no tálamo dorsal. Células ganglionares fotossensíveis da retina, expressando o gene *Brn3b*, enviam informação para o PHb por via independente do SCN. Os neurônios PHb projetam-se para estruturas bem caracterizadas como centros reguladores de humor, como o córtex prefrontal ventral-medial, o corpo estriado dorso-medial e núcleo acumbens (FERNANDEZ *et al*., 2018). Estes dados indicam que o PHb tem papel direto no efeito da luz sobre o humor e aprendizado, sem interferir na atividade do SCN.

Muitos processos estão sob controle circadiano, incluindo o comportamento sono-vigília, secreção hormonal, ciclo celular e expressão gênica (BEDROSIAN; NELSON, 2017). Várias doenças têm sido associadas a perturbações no ritmo circadiano, incluindo doenças psiquiátricas como o transtorno bipolar (BD) (BEDROSIAN; NELSON, 2017; NOVÁKOVÁ *et al.*, 2015; OLIVEIRA *et al.*, 2018; WIRZ-JUSTICE, 2018). De fato, a sazonalidade observada em determinadas doenças, como o Transtorno Afetivo Sazonal (SAD), está diretamente associada à condição fotoperiódica. No SAD, um quadro de depressão é observado com frequência em fotoperíodo curto (inverno), e por vezes, ansiedade em fotoperíodo longo (verão) (BEDROSIAN; NELSON, 2017; GEOFFROY *et al.*, 2014; WIRZ-JUSTICE, 2018).

Perturbações do ritmo circadiano também têm sido observadas em indivíduos com comportamento suicida. Indivíduos classificados com cronotipo vespertino (preferência a desenvolver atividades à tarde/noite) são mais propensos a apresentar maior impulsividade e tentativas de suicídio violentas (SELVI *et al.*, 2011), têm maior propensão ao início do transtorno depressivo maior (SELVI *et al.*, 2010) e maior ideação suicida (BAHK; HAN; LEE, 2014). Indivíduos com comportamento suicida geralmente apresentam distúrbios do sono (PIGEON; PINQUART; CONNER, 2012), genes circadianos já foram identificados entre os principais biomarcadores preditivos de suicidalidade (LEVEY *et al.*, 2016; OLIVEIRA *et al.*, 2018; PAWLAK *et al.*, 2015).

A principal pista para sincronização do ritmo endógeno de plantas e animais a um ambiente cíclico é a luz (BEDROSIAN; NELSON, 2017; LEGATES; FERNANDEZ; HATTAR, 2014). É através do tempo de exposição à luz que se determina o fotoperíodo, composto pela fotofase (fase de claro) e a escotofase (fase de escuro) do ciclo claro/escuro. Assim como o ritmo circadiano é diretamente influenciado pelo regime de fotoperíodo, o ciclo anual de fotoperíodo das estações do ano é o mais importante sincronizador dos ritmos circanuais (cerca de 1 ano), e é provável que esta modulação ambiental do ritmo circadiano tenha papel relevante na formação do comportamento suicida sazonal em indivíduos com vulnerabilidade (WIRZ-JUSTICE, 2018).

Os ritmos circanuais são amplamente distribuídos em plantas e animais, e há muitas evidências mostrando que os humanos apresentam variações sazonais na fisiologia e no comportamento. Dados de expressão gênica em larga escala, em vários países, demonstraram ritmicidade sazonal em genes relacionados à imunidade, fisiologia humana, e inclusive em genes circadianos (DOPICO *et al.*, 2015) (Figura 2A). O estudo de coorte da Alemanha revelou que 23% do genoma codificador de proteínas tem variação sazonal na expressão, sendo 2.311 mRNAs definidos como genes de verão e 2.826 genes de inverno, relacionados a biomarcadores de risco para doenças cardiovasculares, psiquiátricas e autoimunes (DOPICO *et al.*, 2015) (Figura 2B). O mesmo estudo da Alemanha (hemisfério norte, aproximadamente +51° latitude) com genes sazonais foi realizado na Austrália (hemisfério sul, aproximadamente -25° latitude) e mostrou que genes previamente identificados como pertencentes ao verão no hemisfério norte, também foram mais expressos durante o verão do hemisfério sul, indicando tratar-se de um ritmo sazonal, independente do hemisfério (Figura 2C). Curiosamente, na coorte islandesa (+64º latitude), os genes sazonais comuns entre as coortes não compartilham o mesmo padrão de expressão, possivelmente pelo perfil sazonal extremo do país com luz solar de quase 21 horas durante o verão (DOPICO *et al.*, 2015) (Figura 2D).

Mudanças sazonais nos sistemas monoamínicos do cérebro, como a dopamina (EISENBERG *et al.*, 2010; KARSON *et al.*, 1984; NIEOULLON, 2002), serotonina e seus metabólitos (BREWERTON *et al.*, 2018; KANIKOWSKA *et al.*, 2009), transportador de serotonina no cérebro (PRASCHAK-RIEDER *et al.*, 2008; RUHÉ *et al.*, 2009) e neurotrofinas (MOLENDIJK *et al.*, 2012) tem sido relatadas. Esta variação sazonal em moléculas e hormônios pode levar a mudanças no humor e comportamento, como descrito na depressão de inverno do Transtorno Afetivo Sazonal (WIRZ-JUSTICE, 2018), e no transtorno bipolar com fase de mania na primavera/verão e depressão no inverno (GEOFFROY *et al.*, 2014). Avaliações por métodos de imagem também demonstraram variações sazonais na atividade e volume de diferentes regiões do cérebro, mesmo em pessoas saudáveis (MEYER *et al.*, 2016; MILLER *et al.*, 2015).

A importância do fotoperíodo na ritmicidade e comportamento também tem sido estudada em modelos animais (GODA *et al.*, 2015; GREEN *et al.*, 2015; LEGATES; FERNANDEZ; HATTAR, 2014; OTSUKA *et al.*, 2014). Experimentos em camundongos submetidos a diferentes protocolos de fotoperíodo mostraram alterações no perfil de expressão de genes circadianos em SCN (Figura 3) e em outras regiões cerebrais, tanto em fotoperíodo longo quanto curto (DELLAPOLLA *et al.*, 2017; EVANS *et al.*, 2013, 2015; GODA *et al.*, 2015; GREEN *et al.*, 2015; NAGY *et al.*, 2015). No entanto, o efeito fotoperiódico em modelos animais para endofenótipos do comportamento suicida e áreas cerebrais relacionadas ao suicídio, tem sido pouco explorado até o momento, o que nos permitiu avaliar este efeito do fotoperíodo aplicando um protocolo de variação gradual, partindo do fotoperíodo curto ao longo para observar alterações moleculares e comportamentais em camundongos.

A influência fotoperiódica observada em modelos animais (simulando as estações inverno e verão) associada a evidências de que a sazonalidade do suicídio só ocorre em países que estão longe da linha do Equador (AKKAYA-KALAYCI *et al.*, 2017; COIMBRA *et al.*, 2016; FERNÁNDEZ-NIÑO *et al.*, 2016; PETRIDOU *et al.*, 2002; SANTURTÚN; SANTURTÚN; ZARRABEITIA, 2017; TSAI; CHO, 2012), onde o fotoperíodo sofre alteração significativa (variações de fotoperíodo curto x longo), e não em países próximos à linha do Equador, ou seja, um regime de fotoperíodo em torno de 12h:12h claro-escuro (CHEW; MCCLEARY, 1995; PARKER; GAO; MACHIN, 2001; SÁNCHEZ; TEJADA; MARTÍNEZ, 2005), tudo isto vem a indicar um importante papel da luz na sazonalidade do suicídio.

Como o Brasil é um país com grande extensão territorial (incluindo zonas tropicais e temperadas), variando de +5°26' a -33°74' de latitude e -34°82' a -73°97' de longitude, investigamos a influência da latitude na sazonalidade dos suicídios, utilizando o mesmo sistema de notificação de ocorrências e a mesma metodologia de análise rítmica para todos os municípios, o que tende a padronizar os dados e minimizar possíveis erros.

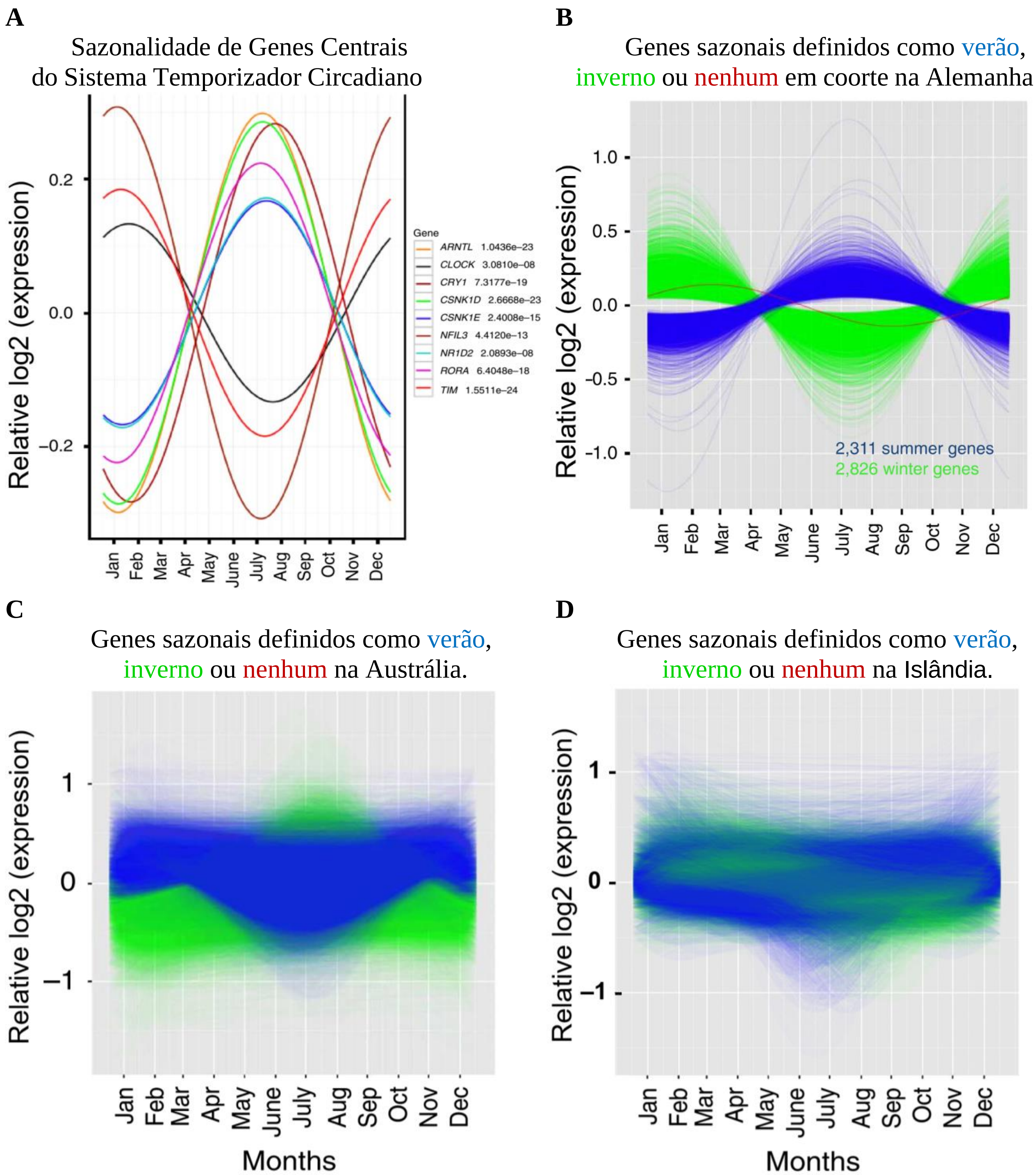

Figura 2. Sazonalidade na expressão de genes em estudos de coorte em 3 países. **A** – Sazonalidade em genes do sistema temporizador circadiano em coorte de crianças da Alemanha (BABYDIET); **B**- Avaliação da sazonalidade do transcriptoma humano na coorte BABYDIET da Alemanha; **C**- Genes previamente identificados como sazonais (BABYDIET) avaliados em coorte australiana; **D**- Perfil dos genes sazonais em coorte na Islândia. Fonte: Dopico *et al.*, 2015.

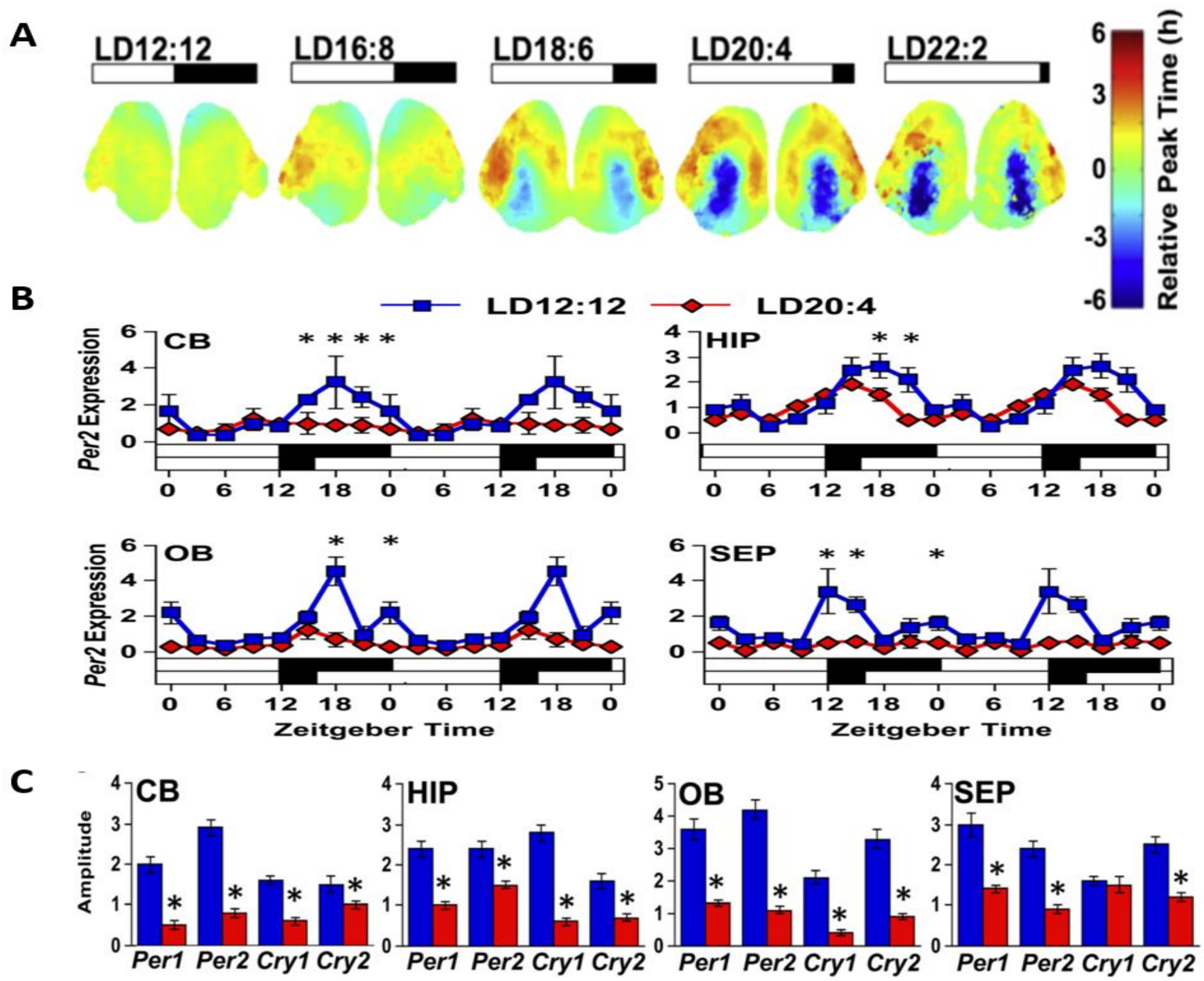

Figura 3. Mudanças fotoperiódicas na organização e função do SCN. A - Média de mapas de fase que ilustram a organização do SCN em condições diferentes de fotoperíodos longos, ressaltando a diferença de expressão de PER2:luciferase no *Shell* e no *Core*. B - A fase dos genes centrais do sistema temporizador circadiano nos tecidos é influenciada pelo fotoperíodo. Os ritmos na expressão de *Per2* foram medidos para cerebelo (CB), hipocampo (HIP), bulbo olfatório (OB) e septo (SEP) sob LD12:12 (quadrados azuis) e LD20:4 (losangos vermelhos). LD *Light-Dark* cycles. Barras brancas e pretas na abscissa representam condições de iluminação (n = 3 / tempo-ponto / fotoperíodo). *LD12:12 versus LD20:4, $p<0,006$. C - A amplitude da expressão dos genes centrais circadiano também está reduzida em todos os quatro tecidos. *Teste t de *Student*, $p<0,05$. Fonte: (EVANS *et al.*, 2013, 2015)

CAPÍTULO 1

"**Do suicide attempts occur more frequently in the spring too? A systematic review and rhythmic analysis**"

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Review article

Do suicide attempts occur more frequently in the spring too? A systematic review and rhythmic analysis

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Background: Seasonal variations in suicides have been reported worldwide, however, there may be a different seasonal pattern in suicide attempts. The aim of this study was to perform a systematic review on seasonality of suicide attempts considering potential interfering variables, and a statistical analysis for seasonality with the collected data.

Method: Observational epidemiological studies about seasonality in suicide attempts were searched in PubMed, Web of Science, LILACS and Cochrane Library databases with terms attempted suicide, attempt and season. Monthly or seasonal data available were evaluated by rhythmic analysis softwares.

Results: Twenty-nine articles from 16 different countries were included in the final review. It was observed different patterns of seasonality, however, suicide attempts in spring and summer were the most frequent seasons reported. Eight studies indicated differences in sex and three in the method used for suicide attempts. Three articles did not find a seasonal pattern in suicide attempts. Cosinor analysis identified an overall pattern of seasonal variation with a suggested peak in spring, considering articles individually or grouped and independent of sex and method used. A restricted analysis with self-poisoning in hospital samples demonstrated the same profile.

Limitations: Grouping diverse populations and potential analytical bias due to lack of information are the main limitations.

Conclusions: The identification of a seasonal profile suggests the influence of an important environmental modulator that can reverberate to suicide prevention strategies. Further studies controlling interfering variables and investigating the biological substrate for this phenomenon would be helpful to confirm our conclusion.

Contents

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1. Introduction

The World Health Organization estimates that 11.4 per 100.000 people (15.0 for males and 8.0 for females) committed suicide around the world in 2012 (WHO, 2014). For every completed suicide there are many more people who attempt suicide every day. Despite sharing the main feature which is the choice of taking their own lives, some studies have described differences between individuals who committed suicide and those who attempted suicide (Dejong et al., 2010; Fushimi et al., 2006; Giner et al., 2013; Malone et al., 2007; Parra Uribe et al., 2013; Younes et al., 2015). Persons who completed suicides were more likely to be male, older, less impulsive, have used more lethal methods, leave a suicide note and tended to be more depressed than low-lethality attempters. Suicide attempters predominantly self-poison, while completed suicides tended to perform hanging and use drugs or firearms. In despite of the proportion of completed suicides be twice higher in men than women, the rate of suicide attempts are more prevalent in women, particularly for young people (Hawton et al., 1998; Iribarren et al., 2000; Parra Uribe et al., 2013; Younes et al., 2015).

It is known that several risk factors act cumulatively to increase vulnerability to suicidal behavior. Some of them are associated with the health system and society, including difficulties in accessing health care, easy access to a mean of suicide such as pesticides or firearms and inappropriate media reporting that sensationalizes suicide. Many other risk factors were reported such as war and disasters, discrimination, sense of isolation, abuse, violence, conflicting relationships, previous suicide attempts, economic crisis, unemployment, chronic pain and a family history of suicide (WHO, 2014).

In despite of many variables that contribute to suicide, a seasonal pattern has been described. In fact, seasonality in completed suicide is a well-known phenomenon and an important topic in epidemiological studies (Ajdacic-Gross et al., 2010; Bridges et al., 2005; Christodoulou et al., 2012; Rasanen et al., 2002; Woo et al., 2012). Interestingly, studies report a higher frequency of suicide in spring and summer (Chew and McCleary, 1995; Christodoulou et al., 2012; Massing and Angermeyer, 1985; Partonen et al., 2004; Petridou et al., 2002; Preti and Miotto, 1998; Rocchi et al., 2007). In a worldwide cross-sectional data from 28 countries, a high frequency of suicides in spring was found (Chew and McCleary, 1995). In some studies, seasonal differences between males and females also have been found: males showing a single peak on spring, while females two peaks, in spring and autumn (Lester and Frank, 1988; Meares et al., 1981; Micciolo et al., 1989; Yip et al., 2000). The reason for this seasonal variation in completed suicides remains unclear.

Seasonal variation does not exist only in completed suicides. A similar pattern was also reported in attempted suicides (Yip and Yang, 2004). However, some studies described attempted suicide peaks in autumn and/or winter (Chien et al., 2013; Elisei et al., 2012; Pajoumand et al., 2012; Wenz, 1977a). Moreover, studies suggest that this seasonality might be a sex-specific phenomenon (Barker et al., 1994; Masterton, 1991; Mergl et al., 2010). Some researchers showed evidences of seasonality only in women (Barker et al., 1994; Jessen et al., 1999; Masterton, 1991). The reasons for this sex difference also remain unknown, but a possible explanation could be associated with the choice of the method used (Rock et al., 2005; Yip and Yang, 2004). There is no consensus in studies regarding seasonality of suicide attempts and, to our knowledge, no systematic review in this topic has been published.

The research question of this study was to know whether suicide attempts occur more frequently in the spring, such as already described for completed suicides. Thus, a systematic review of articles reporting suicide attempts over the year, in many countries, was conducted to investigate which season presents the higher incidence, considering potential interfering variables, such as sex, type of method used and source of data. Also, we performed a statistical analysis for seasonality with the collected data using applicable methods for rhythmic phenomena. The identification of a global seasonal profile in suicide attempts would provide knowledge to guide governments and public health organizations to develop strategies that can prevent suicide effectively.

2. Material and methods

The guidelines provided by the PRISMA statement (Moher et al., 2009) were closely applied. The searches were conducted in the following databases: Medline (Medical Analysis and Retrieval System Online) via PubMed (1966 to September 2014), ISI Web of Science (1945 to September 2014), LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde) (1982 to September 2014) and Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 8, 2014). The searches were limited to articles published in the last four decades. We used the search terms “attempted suicide”, “attempt”, “season” to search all databases. In Pubmed, the search strategy was: (“suicide, attempted” [MeSH Terms] OR (“suicide” [All Fields] AND “attempted” [All Fields]) OR “attempted suicide” [All Fields] OR (“attempt” [All Fields] AND “suicide” [All Fields]) OR “attempt suicide” [All Fields]) AND (“seasons” [MeSH Terms] OR “seasons” [All Fields] OR “season” [All Fields]).

Inclusion criteria consisted of studies investigating seasonality (season or month of occurrence described) in attempted suicides. Exclusion criteria consisted of studies reporting suicide data, without suicide attempt information and/or lack of data regarding seasonality. Searches were limited to articles published in English, Portuguese and Spanish in peer-reviewed journals. Five authors (ACPS, DGC, DSF, JLAS and MRB) reviewed the titles and abstracts for eligibility, documenting the reason for exclusion of each trial (Fig. 1). Then, authors jointly selected studies for detailed extraction on the basis of the full abstract. If abstract was unavailable, the article was automatically excluded. Additional articles were identified through the reference lists of the retrieved articles. Disagreements between reviewers were resolved by consensus.

A specific data extraction form was created to collect the following information from each study: type of study, objectives, main characteristics, country/state studied, sample size, study period, sex differences, seasonal distribution (seasons or months), the classification of season used, method used to attempt suicide, source of data, relationship with meteorological parameters and approximate distance from the equator line.

By convention, throughout this paper we used “seasonal” or “seasonality” to indicate the month or climatic seasons during the year. The term “suicide attempt” refers to intentional self-inflicted poisoning, injury or self-harm which have a fatal intent without death. In order to standardize the data, definition of season of each article was evaluated and categorized. The data from seasons were

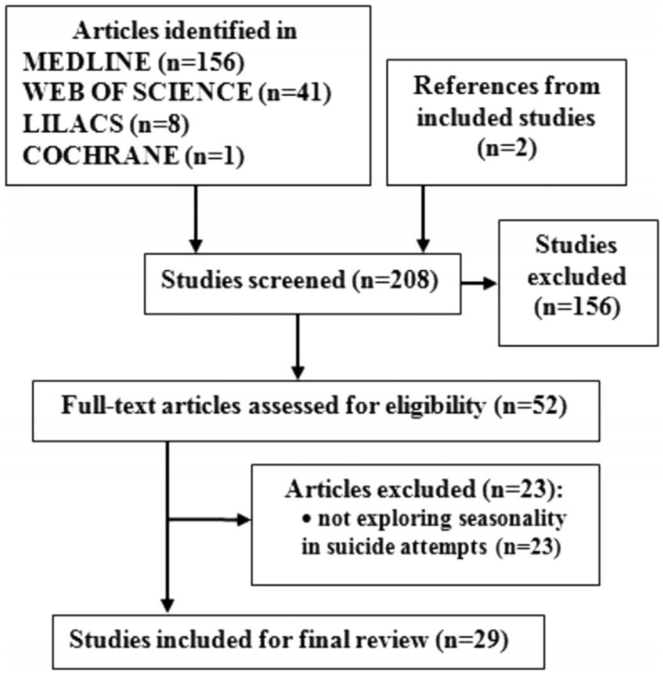

Fig. 1. The study flow chart.

classified as calendric (Spring in March 1 to May 31; Summer in June 1 to August 31; and go on in Northern Hemisphere) and astronomic (using equinox and solstice).

Absolute or average data of suicide attempts available from each month or season were extracted from text, tables and figures. A circannual (12-month) cycle was assumed to establishing a seasonal pattern. Data restricted to four seasons (autumn, winter, summer and spring) were also evaluated. A statistically significant variation in cosinor to identify rhythmicity in suicide attempts over the year was the primary measure to determine seasonality.

CircWave version 1.4 (http://www.euclock.org/results/item/circ-wave.html) was applied to perform cosinor and Fourier analysis in monthly data. Since CircWave input requires at least six temporal data series, we used Acro version 3.5 (http://www.circadian.org/softwar.html) for those data consisting of just four seasons. Acro software calculates cosinor and generates a fitted curve (Refinetti et al., 2007), however does not perform Fourier test. Acrophase (point in the curve with the highest value) and amplitude (difference between the achophase value and mean value) were calculated by CircWave and Acro programs in each case.

To perform rhythmic analysis grouping data from different studies in Acro or CircWave, each value was converted into fold change to minimize the mean's deviation discrepancy between articles. Fold changes were calculated dividing the values of each month by the first month of winter (for articles with 12 months) or each season by the winter season. This strategy reduces the heterogeneity while maintains the same oscillatory data profile. Amplitude was also calculated from fold change values for the same reason. Kruskal–Wallis test was also performed as alternative method to analyze data in more than two groups. Spearman's coefficient (rho) was used to evaluate the correlation between the data from males and females. For all analyzes, a $p < 0.05$ was considered statistically significant. Charts and analysis were generated using Graphpad Prism version 5.00 software.

We used the Quality Criteria Checklist: Primary Research (Dietitians Association of Australia, 2011), a standardized quality assessment checklist which evaluates aspects related to study design, statistical methodology and reporting quality, and could be used in reports where there are no interventions (Hunt et al., 2015). Assessment of the analytical methodology was determined independently by four authors (ACPS, DSF, TGA and VMA). The percentage of agreement between co-authors was 80% and discordant evaluations were discussed until consensus was achieved.

3. Results

The electronic searches yielded 208 potentially relevant studies that were selected for titles and abstracts reading. A flow chart demonstrating the process for selecting relevant articles is showed in Fig. 1. After examining the titles and abstracts, 156 articles were excluded (02 in Polish and 02 in German). Twenty-three articles did not deal with seasonality or differentiate attempted suicide and suicide. Only 29 studies satisfied all criteria and were extensively analyzed (Table 1).

As shown in Table 2, the quality assessment found that 20 (69.0%) studies had an overall positive quality ratings according to the Quality Criteria Checklist: Primary Research. The other 09 (31.0%) studies had neutral quality ratings for failing to meet the requisites of items 2 and 6, although the majority of the other answers are adequate. Four studies received a negative rating because the research question was not clearly stated, four studies were not free from bias, and sixteen did not describe the method of handling withdrawals. In four articles, procedures were not described in details and eight failed to adequately discuss biases and limitations.

All articles reviewed were cross-sectional studies, with only two exceptions, a prospective study of case series (Hatzitolios et al., 2001) and a case–control study (Al-Ansari et al., 1997). The studies from 16 different countries were analyzed. The majority of them were from European countries with five in Turkey (Akbaba et al., 2007; Aydin et al., 2013; Doganay et al., 2003; Seydaoglu et al., 2005; Tufekci et al., 2004), three in Italy (Elisei et al., 2012; Preti, 1997; Preti and Miotto, 2000), one in each country: British (Barker et al., 1994), Czech Republic (Zakharov et al., 2013), Finland (Valtonen et al., 2006), Germany (Mergl et al., 2010), Greek (Hatzitolios et al., 2001), Republic of Macedonia (Polazarevska et al., 2011) and Scotland (Masterton, 1991). Six studies from Asian countries were included (Al-Ansari et al., 1997; Chien et al., 2013; Islambulchilar et al., 2009; Pajoumand et al., 2012; Saadat, 2005; Yip and Yang, 2004); five Americans (Beauchamp et al., 2014; Geltzer et al., 2000; Nakamura et al., 1994; Wenz, 1977a, 1977b). In Africa, one in South African (Minnaar et al., 1980) and one in African coast near the tropic of cancer (Santana Cabrera et al., 2010). One study was conducted in Australia (Rock and Hallmayer, 2008). Only the studies of Minnaar et al., 1980 and Rock and Hallmayer, 2008 were performed in southern hemisphere.

The overall sample size in the current review was 1,227,437 suicide attempts, with a minimum of 67 (Al-Ansari et al., 1997) and a maximum of 1,065,067 participants (Beauchamp et al., 2014). The study period ranged from 1 (Al-Ansari et al., 1997; Elisei et al., 2012; Minnaar et al., 1980; Tufekci et al., 2004; Valtonen et al., 2006; Wenz, 1977b) to 20 years (Preti, 1997). The information of suicide attempt was provided by admission in hospitals in 21 (72.4%) cases, two cases from national institutes of statistical analysis (Preti, 1997; Preti and Miotto, 2000), telephone calls to poison center hot-lines (Beauchamp et al., 2014; Zakharov et al., 2013) and others from several sources (Aydin et al., 2013; Mergl et al., 2010; Wenz, 1977a, 1977b).

Statistical correlation with meteorological variables was evaluated in five articles (Barker et al., 1994; Doganay et al., 2003; Geltzer et al., 2000; Preti, 1997; Preti and Miotto, 2000). Three authors indicated correlation with suicide attempts and high temperatures (Barker et al., 1994; Doganay et al., 2003; Preti and Miotto, 2000). There was divergence between the author's results

Table 1
Characteristics of the studies included in the systematic review.

Study	Population	Sample size	Study period	Seasonal distribution		Remarks
				Female	Male	
Santana Cabrera et al., 2010	African coast, near the tropic of Cancer	132	2001–2008	No differences between sex. peak: spring		Patients admitted to the emergency room in a Hospital by self-poisoning.
Minnaar et al., 1980	South Africa, Durban	310	January–December 1978.	Sex differences were not evaluated. Peak: spring and summer		Analyzed 310 patients attended at Addington Hospital Durban involved with overdose, poisoning, self-inflicted injury and other possible manifestations of parasuicide. Self-poisoning occurred in 79.0% cases.
Al-Ansari et al., 1997	Arabian gulf, Bahrain	67	June 1993 to December 1994	Sex differences were not evaluated. Peak: summer		A case–control study of 67 overdose attempts among youth (15 – 24 years) admitted in three hospitals: Salmaniya medical center, Bahrain defense force Hospital and the psychiatric Hospital.
Rock and Hallmayer, 2008	Western Australia	16,619	1984–1993	Peak in Spring/early summer. "in the UK migrants, this seasonality is only associated with females".		Seasonal risk factors for self-harm in three different population birth groups living in western Australia: Australian Aborigines, Australian born non-Aborigines, and UK migrants. Data extracted from western Australian Hospital case register.
Barker et al., 1994	British	12,379	January 1976–December 1989	Spring and summer	No seasonality.	Tested whether parasuicide admission rate is related to weather variables. Admission at the general Hospital in Oxford following deliberate self poisoning and self-injury. Weather had a small influence on parasuicide. Sex differences in body temperature regulation might account for the sex difference seen.
Yip and yang, 2004	China, Hong Kong	10,376	1997–2001	Spring (May) and a minor peak in autumn (October).	No significant.	Examined seasonal variation between suicide deaths and attempts simultaneously. patients admitted at the Hospital authority with diagnosis of deliberate self-harm identified as attempted suicide.
Chien et al., 2013	China, Taiwan	1004	2005–2008	Sex differences were not evaluated. Peak: autumn to repeated suicide attempts and Spring to non-repeated suicide attempts.		Subjects at Taiwan's national health insurance research database were selected, which were hospitalized due to repeated suicide attempts. most of suicide attempts were by self-poisoning (58.2%).
Zakharov et al., 2013	Czech republic, Prague	2393	2007–2011	Not conclusive.	Peak: spring. May (highest), September (lowest).	Calls to Czech Toxicological information center (TIC) regarding suicidal attempts by self-poisoning by children between 9 and 13 years old and by adolescents between 14 and 18 years old were selected for further analysis.
Valtonen et al., 2006	Finland, Helsinki	1636	January 1997–January 1998.	Peak at end of summer/begin of autumn (September) and lowest in winter (February).	Peak at summer (August).	All suicide attempts of Helsinki residents aged 15 years ormore admitted to health care during the study period. the data were gathered from all four of the city's general hospitals treating suicide attempters: two university clinics and two municipal hospitals. Self-poisoning occurred in 89.5%.
Mergl et al., 2010	Germany	2269	2000–2004	Non-violent methods had a trough in Spring	No seasonality was found.	Analyzed the association of sex with seasonality in suicide attempts by persons living in two northern Bavarian regions: nuremberg and region of Wuerzburg. (patients > 18 years old). Data were obtained in cooperation with the hospitals in these cities, a representative sample of psychiatric practices, crisis intervention centers and local authorities. Self-poisoning occurred in 84.7%.
Hatzitolios et al., 2001	Greek	273	January 1998–December 2000.	Sex differences were not evaluated. Peak: Summer Nadir: Spring		Studied the epidemiology of acute poisoning patients presenting to an acute medical service ward in a Greek Hospital. design of study: prospective case series.
Pajoumand et al., 2012	Iran	6414	1997–2007	Peak: May (Spring)	Peak: December (autumn/winter)	Hospitalized patients at poison center of Loghman-Hakim Hospital at ages 8–16, WHO attempted suicide were investigated (91.7% drug administration).
Saadat, 2005	Iran, Kohgiluyeh Va	86	July 2002–July	No seasonal variation was found.		Patients admitted to the burn unit of Shahid Beheshti

	Boyer Ahmad		2004			Hospital (Yasuj) by self-inflicted burns.
Islambulchilar et al., 2009	Iran, Tabriz	1210	June 2003–July 2005	Sex differences were not evaluated. peak: spring		Investigated the etiological and demographical characteristics of acute adult poisoning cases admitted to a university Hospital in Tabriz. The mean age was 26.8 ± 12.6 years (age range 8–90) and the majority of the patients (79.4%) were less than 30 years.
Elisei et al., 2012	Italy	111	2011–2012	Sex differences were not evaluated. Peak: January (winter)		Suicide attempters were recruited in the emergency department of the Santa maria della Misericordia, Perugia, Italy. Age: mean 42.9 ± 14.8 (range 17 – 89). Drug overdose occurred in 53.2% cases.
Preti and Miotto, 2000	Italy	27,456	1984–1995	Violent attempted suicides show a slight 4-monthly trend, whereas non-violent attempts show no seasonal trend at all.	Violent attempted suicides: peak in Spring and Nadir in autumn. Non-violent attempts: slight peak in late winter.	Data were taken from the Istituto Italiano DI Analisi Statistiche (ISTAT). Verified IF attempted suicides follow different seasonal distributions according to the method chosen, studying the monthly distribution of admissions, according to sex and age, distinguishing between non-violent and violent attempted suicides. Age of participants ranged of from 14 to 65 years and above. Among males, higher temperatures positively correlate with attempted suicides, whereas cooler temperatures seem to exert a protective action. Female attempts show a less evident correlation with indicators of temperature. The age groups with most attempts (25–44 and 45–64 years old) do not show evidence of seasonality. Self-poisoning have the highest frequency among men and women.
Preti, 1997	Italy	46,869	1974–1994	No differences between sex. Peak: Spring Nadir: Autumn		Data were taken from the Istituto Italiano DI Analisi Statistiche (ISTAT). Studied the relationship between some climatic factors and suicide and attempted suicide rates. The monthly distribution of suicide deaths and of attempted suicides follows a significant direct relationship with exposure to Sun, and an inverse relationship with rainfall levels.
Polazarevska et al., 2011	Republic of Macedonia, Skopje	1683	1999–2008	No statistical difference in the distribution by sex and months. peak: end Spring/begin summer. Higher average occurred in June and July.		Admission to the university clinic of toxicology and emergency medicine in Skopje. The most common method of suicide attempt was intoxication with medications. The age of male patients varied in the range of 40.25 ± 14.87 years and female ranged 38.04 ± 15.62 years (14 to 95 years). Self-poisoning occurred in 53.2% cases.
Masterton, 1991	Scotland, Edinburgh	22,169	January 1969–December 1987	Peak: spring and summer. Nadir: Winter (December).	No monthly or seasonal variation.	Observed a parasuicide sex difference in monthly and seasonal variation. Patients with 16 years of age OR older admitted at regional poisoning treatment center at the royal infirmary were included.
Akbaba et al., 2007	Turkey	427	January–December 2004.	Sex differences were not evaluated. Peak: Summer; Nadir: Winter		Studied the etiological and demographical characteristics of the patients applying to the emergency department in faculty of medicine Çukurova university because of poisoning. average age of men was 27.1 ± 10.5 years and that of women was 24.4 ± 9.5 years.
Doganay et al., 2003	Turkey	1119	1996–2001	No differences between sex. Peak: particularly in summer and less in the Spring.		The data were obtained retrospectively from the folders of patients WHO were admitted to Ondokuz Mayis university Hospital ED. relationship between climatic factors and suicidal behavior. A clear seasonal variation was seen in the 15 – 24, 25 – 34, and over 65 age groups in men and in the 15 – 24, 25 – 34, and 35 – 44 age groups in women with peaks in the spring and summer. People attempting suicide WHO have depression, anxiety, OR a psychotic disorder usually attempt suicide in the summer. Whereas the monthly averages of Humidity, ambient temperature, duration and intensity of sunlight were positively correlated with the number of monthly suicide attempts, cloudiness and atmospheric pressure were negatively correlated. Self-poisoning occurred in 92.9% cases.

Table 1 (*continued*)

Study	Population	Sample size	Study period	Seasonal distribution		Remarks
				Female	Male	
Seydaoglu et al., 2005	Turkey	2229	1997–2002	Sex differences were not evaluated. Peak: spring and summer		Evaluated the data on acute adult poisoning at a university emergency department in Turkey and identify the risk factors of mortality. Mean age was 29.3 ± 13.2 for males and 23.8 ± 9.6 for females. pesticides were the most frequent method of suicide attempt (58.7%).
Tufekci et al., 2004	Turkey, Istanbul	204	January 2001–2005 December 2001	Sex differences were not evaluated. Peak: summer and winter		Analyzed the characteristics of acute adult poisoning cases admitted to the Istanbul university Cerrahpasa medical faculty Hospital. the mean age was 27 ± 12 years (age range 15 – 87).
Aydin et al., 2013	Van,Turkey	1323	2007–2010	No seasonal variation was found. No differences between sex.		Data were extracted from the local service of the ministry of health (private and public hospitals, and security units, including police stations and military units all over the city). In despite of not having found seasonality, a group of illiterate individuals were more prone to commit suicidal in summer. Drug or substance intoxication was the most frequent method of suicide attempt.
Beauchamp et al., 2014	USA	1,065,067	2006–2010	Sex differences were not evaluated. Peak: spring and autumn.		Determined if particular days of the week, seasons, or holidays were associated with increased attempted and completed suicides by poisoning. All calls about suicide attempts by poisoning reported to the national poison data system (NPDS) were analyzed. New Year's Day had a Higher number of exposures, whereas independence Day, thanksgiving, and Christmas had fewer exposures. Mean age total (years) 32.1 ± 14.2.
Wenz, 1977a	USA, Michigan	2942	1970–1974	No differences between sex. Peak: Autumn/Winter (December); Nadir: Summer (August)		The cases were recorded by the police, public and private hospitals, and information supplied by physicians. Investigated the relationship between the timing of completed suicide, attempted suicide and the sociological variables of sex, race, age, marital status and occupation.
Geltzer et al., 2000	USA, Washington	264	1981–1995	Sex differences were not evaluated. Peak: march (end of winter/begin of spring)		Patients admitted at Virginia mason medical center in Seattle for treatment of intentional carbon monoxide (CO) poisoning. No other weather variables showed significant correlation with data of CO suicide attempts.
Nakamura et al., 1994	USA, Honolulu, Hawaii	296	1987–1991	No seasonal variation was found. No differences between sex.		Patients admitted in two hospitals. only adolescents were analyzed (age 12 – 18). Monday and Tuesday were with Higher chance to attempt (39% of attempts). attempts occur during afternoon/evening. drug overdose was 85%.
Wenz, 1977b	USA, South Carolina	110	December 1973 – November 1974	Sex differences were not evaluated. Peak: spring		Cooperation of physicians in the community, the police department, and the suicide prevention center. all selected subjects were interviewed and given a questionnaire within 3 week after suicidal crisis. A comparison of mean scale scores for actual and future loneliness by season shows seasonality.

Table 2
Study quality ratings according to the quality criteria checklist: primary research.

Quality criteria checklist	Questions										Overall quality
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	
Akbaba et al., 2007	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Al-Ansari et al., 1997	Y	Y	NA	N	NA	N	Y	N	Y	Y	NE
Aydin et al., 2013	Y	Y	NA	N	NA	Y	Y	Y	Y	Y	P
Barker et al., 1994	Y	Y	NA	N	NA	Y	Y	Y	Y	Y	P
Beauchamp et al., 2014	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Santana Cabrera et al., 2010	Y	Y	NA	N	NA	Y	Y	N	N	Y	NE
Chien et al., 2013	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Doganay et al., 2003	Y	Y	NA	Y	NA	Y	Y	Y	N	Y	P
Elisei et al., 2012	N	Y	NA	N	NA	Y	Y	N	N	Y	P
Geltzer et al., 2000	Y	Y	NA	N	NA	Y	Y	Y	Y	Y	P
Hatzitolios et al., 2001	Y	Y	NA	Y	NA	Y	Y	Y	N	Y	P
Islambulchilar et al., 2009	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Masterton, 1991	N	Y	NA	N	NA	Y	Y	Y	N	Y	P
Mergl et al., 2010	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Minnaar et al., 1980	N	Y	NA	Y	NA	Y	Y	Y	N	Y	P
Nakamura et al., 1994	Y	Y	NA	N	NA	N	Y	Y	Y	Y	NE
Pajoumand et al., 2012	Y	Y	NA	N	NA	Y	Y	N	Y	Y	P
Polazarevska et al., 2011	Y	N	NA	N	NA	Y	Y	Y	Y	Y	NE
Preti and Miotto, 2000	Y	Y	NA	Y	NA	Y	Y	Y	N	Y	P
Preti, 1997	Y	Y	NA	N	NA	Y	Y	Y	N	Y	P
Rock and Hallmayer, 2008	Y	Y	NA	N	NA	Y	Y	Y	Y	Y	P
Saadat, 2005	N	N	NA	N	NA	Y	Y	Y	Y	Y	NE
Seydaoglu et al., 2005	Y	N	NA	Y	NA	Y	Y	Y	Y	Y	NE
Tufekci et al., 2004	Y	Y	NA	N	NA	N	Y	N	Y	Y	NE
Valtonen et al., 2006	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Wenz, 1977a	Y	Y	NA	N	NA	N	Y	Y	Y	Y	NE
Wenz, 1977b	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P
Yip and yang, 2004	Y	N	NA	N	NA	Y	Y	Y	Y	Y	NE
Zakharov et al., 2013	Y	Y	NA	Y	NA	Y	Y	Y	Y	Y	P

Questions:
1. Was the research question clearly stated?
2. Was the selection of study subjects free from bias?
3. Were study groups comparable?
4. Was method of handling withdrawals described?
5. Wwas blinding used to prevent introduction of bias?
6. Were procedures described in detail?
7. were outcomes clearly defined and the measurements valid and reliable?
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?
9. Were conclusions supported by results with biases and limitations taken into consideration?
10. Is bias due to study's finding or sponsorship unlikely?

Y, Yes; N, No; NA, not applicable; P, positive; NE, neutral.

in which low temperatures, rain, cloud and humidity, indicate a protective factor or a risk factor depending on the study. Daylight duration and sunlight exposure have been shown in two articles as risk factors (Doganay et al., 2003; Preti, 1997). A significant increase in overall suicide attempt numbers was observed on the day after following thunder or high temperatures (Barker et al., 1994).

All reports have indicated a higher frequency of suicide attempts in women; except for one which did not report whether there was a sex difference (Geltzer et al., 2000) and other reporting higher frequency of suicide attempts in men (Santana Cabrera et al., 2010).

Seventeen articles described the calendrical classification for the definition of season. Ten articles did not reported how season was classified (Akbaba et al., 2007; Al-Ansari et al., 1997; Santana Cabrera et al., 2010; Hatzitolios et al., 2001; Islambulchilar et al., 2009; Rock and Hallmayer, 2008; Saadat, 2005; Seydaoglu et al., 2005; Tufekci et al., 2004; Wenz, 1977b), one used the astronomical classification (Nakamura et al., 1994) and one adapted the astronomical definition to Summertime (Equinox and Solstice) and Wintertime (Solstice to Equinox) (Valtonen et al., 2006).

The patterns of seasonality reported across the studies are presented in Tables 1 and 3. Twenty-six (89.6%) studies identified seasonality in suicide attempts. Only three articles did not find seasonality (Aydin et al., 2013; Nakamura et al., 1994; Saadat, 2005). Suicide attempts in spring and summer were the most frequent seasons reported. When sexes were considered, the most common seasons were spring and summer for both. Eight studies found differences in seasonality between males and females (Barker et al., 1994; Masterton, 1991; Mergl et al., 2010; Pajoumand et al., 2012; Preti and Miotto, 2000; Valtonen et al., 2006; Yip and Yang, 2004; Zakharov et al., 2013). Mergl et al. (2010), did not report a seasonal peak, but only a trough in spring for females. Twelve studies did not report information regarding sex differences in seasonality (Akbaba et al., 2007; Al-Ansari et al., 1997; Beauchamp et al., 2014; Chien et al., 2013; Elisei et al., 2012; Geltzer et al., 2000; Hatzitolios et al., 2001; Islambulchilar et al., 2009; Minnaar et al., 1980; Seydaoglu et al., 2005; Tufekci et al., 2004; Wenz, 1977b).

When applying methods for the analysis of rhythmic patterns to each article, the peak (acrophase) of suicide attempts was most frequent in spring (Table 3). Three articles presented a significant peak in winter (Nakamura et al., 1994; Wenz, 1977a; Wenz, 1977b) and one in summer (Minnaar et al., 1980). In five articles, we identified seasonality in suicide attempts in just one sex, all acrophases ranging from mid-spring to mid-summer (Barker et al., 1994; Santana Cabrera et al., 2010; Masterton, 1991; Mergl et al., 2010; Pajoumand et al., 2012). Preti and Miotto, 2000 and Yip and Yang, 2004 reported seasonality (spring peak) in suicide attempts in just one sex. Nevertheless, we identified seasonality also in the other sex, with a peak in spring for females (Preti and Miotto, 2000) and summer for males (Yip and Yang, 2004). Mergl et al. (2010) did not detected seasonality in their data, however, our analysis indicated an acrophase in summer for males. The data obtained from Valtonen et al. (2006) could not be analyzed by any test due to the classification method used, and in Rock and Hallmayer (2008) no data was presented, only a report of seasonality in spring/early summer.

The majority of papers do not present individual original data, just the sum of suicide attempts per month or means (only Polazarevska, 2011-presented individual original data; Barker et al., 1994; Geltzer et al., 2000; Beauchamp et al., 2014–presented data as means). We also re-analyzed the data excluding the 3 articles with average data to observe if they were contributing to the outcome. Both results showed similar profiles (data not shown).

Twenty-three articles showed a higher frequency of self-poisoning/intoxication by drugs compared to other methods. One study reported self-inflicted burns (Saadat, 2005) and other reported carbon monoxide poisoning (Geltzer et al., 2000) as the methods used. However, only three articles analyzed the seasonality of suicide attempts in relation to methods, one grouped in violent and non-violent methods (Yip and Yang, 2004), and two described each method separately (Doganay et al., 2003; Preti and Miotto, 2000). Five studies did not describe the method used for suicide attempt (Barker et al., 1994; Preti, 1997; Rock and Hallmayer, 2008; Wenz, 1977a; 1977b). Rhythmic analysis applied on data obtained from articles exhibited seasonal profile mainly for spring both for violent and non-violent methods (Table 4).

Fig. 2A shows the analysis of 11 articles with data per month and grouped by season, resulting in a significant seasonal variation with acrophase at mid-late spring (Barker et al., 1994; Elisei et al., 2012; Geltzer et al., 2000; Masterton, 1991; Minnaar et al., 1980;

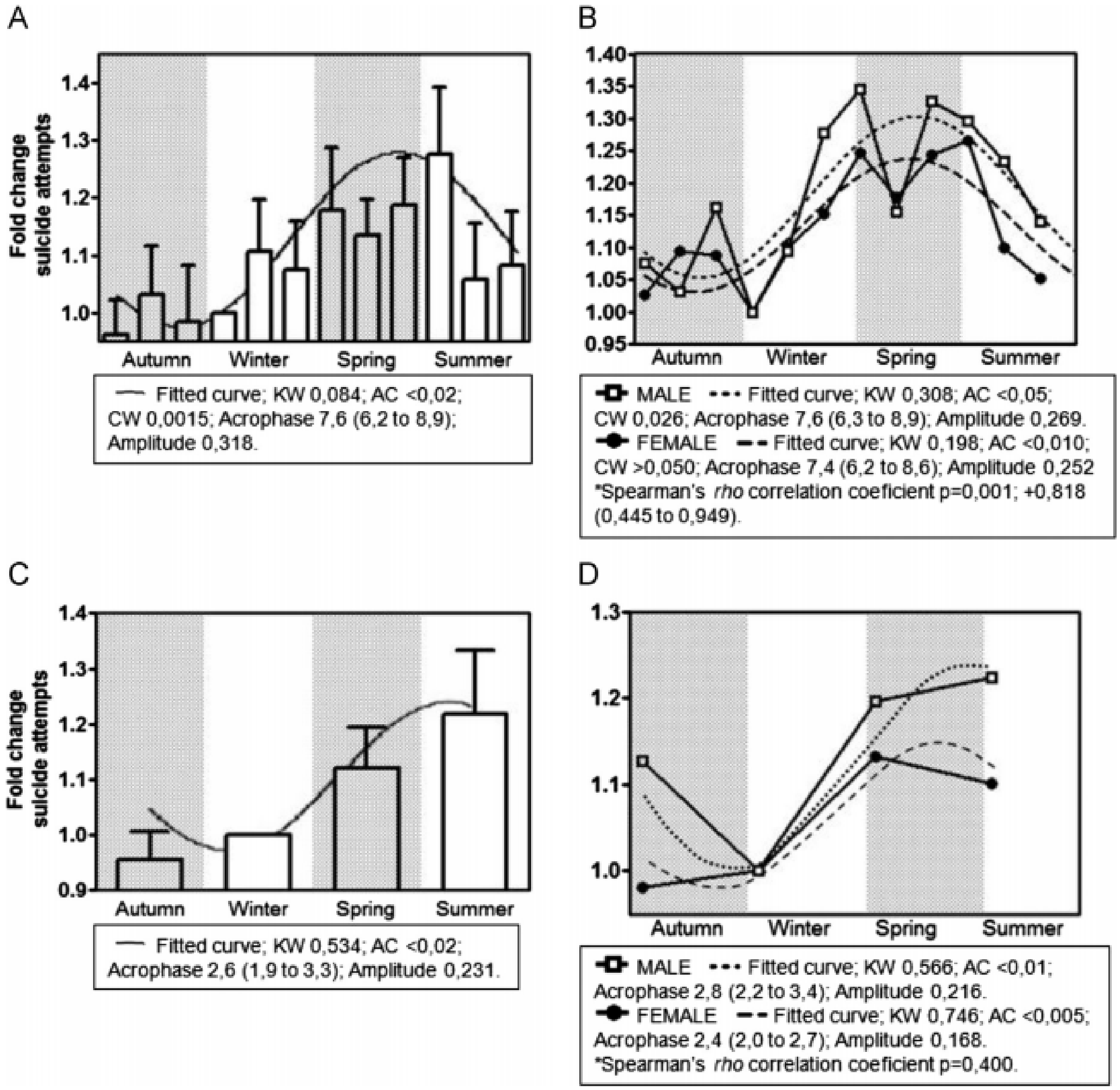

Fig. 2. Observed (bars and symbols) and estimated (fitted curve) distribution of suicide attempts among studies analyzed as a group. A–Seasonal distribution of monthly data from 11 articles (Barker et al., 1994; Elisei et al., 2012; Geltzer et al., 2000; Masterton, 1991; Minnaar et al., 1980; Pajoumand et al., 2012; Polazarevska et al., 2011; Preti and Miotto, 2000; Wenz, 1977a; Yip and Yang, 2004; Zakharov et al., 2013). B–Monthly distribution of 7 articles separated by sex (Barker et al., 1994; Masterton, 1991; Pajoumand et al., 2012; Polazarevska et al., 2011; Preti and Miotto, 2000; Yip and Yang, 2004; Zakharov et al., 2013). C–Pattern observed for 20 articles with data restricted to seasons (Akbaba et al., 2007; Al-Ansari et al., 1997; Aydin et al., 2013; Barker et al., 1994; Beauchamp et al., 2014; Santana Cabrera et al., 2010; Chien et al., 2013; Doganay et al., 2003; Hatzitolios et al., 2001; Islambulchilar et al., 2009; Masterton, 1991; Mergl et al., 2010; Nakamura et al., 1994; Saadat, 2005; Seydaoglu et al., 2005; Pajoumand et al., 2012; Preti, 1997; Tufekci et al., 2004; Wenz, 1977a, 1977b). D–Seasonal distribution by sex of 8 articles with data restricted to seasons (Barker et al., 1994; Santana Cabrera et al., 2010; Doganay et al., 2003; Masterton, 1991; Mergl et al., 2010; Pajoumand et al., 2012; Preti, 1997; Wenz, 1977a). KW–Krukal Wallis test; AC–Acro; CW–Circwave. Acrophase value: Month (0 to 2-Autumn, 3–5-Winter, 6–8-Spring, 9–11-Summer) or Season (0-Autumn, 1-Winter, 2-Spring, 3-Summer). Bars plotted in mean with SEM. 95% confidence interval in round brackets.

Pajoumand et al., 2012; Polazarevska et al., 2011; Preti and Miotto, 2000; Wenz, 1977a; Yip and Yang, 2004; Zakharov et al., 2013). The same pattern of seasonality was observed when data were distributed by sex (Barker et al., 1994; Masterton, 1991; Pajoumand et al., 2012; Polazarevska et al., 2011; Preti and Miotto, 2000; Yip and Yang, 2004; Zakharov et al., 2013), with a strong correlation (*rho* + 0.818 p = 0.001) between groups (Fig. 2B). Kruskall-Wallis test did not identify any significant difference between groups.

Twenty articles with information restricted to seasons were grouped (Akbaba et al., 2007; Al-Ansari et al., 1997; Aydin et al., 2013; Barker et al., 1994; Beauchamp et al., 2014; Santana Cabrera et al., 2010; Chien et al., 2013; Doganay et al., 2003; Hatzitolios et al., 2001; Islambulchilar et al., 2009; Masterton, 1991; Mergl et al., 2010; Nakamura et al., 1994; Saadat, 2005; Seydaoglu et al., 2005; Pajoumand et al., 2012; Preti, 1997; Tufekci et al., 2004; Wenz, 1977a; 1977b), also resulting in a seasonal variation with acrophase at mid-late spring, similar to that observed for 12 month data (Fig. 2C). When sex was considered (Barker et al., 1994; Santana Cabrera et al., 2010; Doganay et al., 2003; Masterton, 1991; Mergl et al., 2010; Pajoumand et al., 2012; Preti, 1997; Wenz, 1977a), both data from males and females showed seasonality with acrophase in mid-late spring (Fig. 2D).

In order to reduce the heterogeneity between studies, we also performed an analysis restricting the data by both source and specific method, including only articles with data originated from hospitals (community data were not used) and from individuals who attempted suicide by self-poisoning. Four articles with data per month were selected (Masterton, 1991; Pajoumand et al., 2012; Polazarevska et al., 2011; Yip and Yang, 2004), showing acrophase in late spring, for both males and females (Fig. 3A). Data from eight

Table 3
Seasonal variation of suicide attempts analyzed by rhythmic methods.

	Studies	Peak reported	Rhythmic analysis			
			Season	Acroph[a]	Amplitude	Method[b]
4 Seasons						
Females	Santana Cabrera et al. (2010)[e]	–	SP	2.4	0.45	AC
	Doganay et al. (2003) [c]	SP, SU	SP	2.7	0.37	AC
	Mergl et al. (2010)[c]	–	–	–	–	–
	Preti (1997)[c]	SP	SP	2.0	0,01	AC
	Wenz (1977)(a)[c]	WI	WI	1.1	0,15	AC
Males	Santana Cabrera et al. (2010)[e]	–	–	–	–	–
	Doganay et al. (2003) [c]	SP, SU	SP	2.9	0.94	AC
	Mergl et al. (2010) [c]	–	SU	3.0	0.06	AC
	Preti (1997) [c]	SP	SP	2.0	0.10	AC
	Wenz (1977)(a) [c]	WI	WI	1.0	0.22	AC
Not evaluated by sex	Akbaba et al. (2007) [e]	SU	SP	2.9	0.36	AC
	Al-Ansari et al. (1997)[e]	SU	–	–	–	–
	Aydin et al. (2013) [c]	–	–	–	–	–
	Beauchamp et al. (2014) [c]	AU, SP	–	–	–	–
	Chien et al. (2013)[c]	AU	–	–	–	–
	Hatzitolios et al. (2001) [e]	SU	SP	2.7	0.77	AC
	Islambulchilar et al. (2009) [e]	SP	SP	2.3	0.15	AC
	Nakamura et al. (1994) [d]	–	WI	1.3	0.07	AC
	Saadat (2005) [e]	–	–	–	–	–
	Seydaoglu et al. (2005) [e]	SU	SP	2.8	0.27	AC
	Tufekci et al. (2004) [e]	SU	–	–	–	–
	Wenz (1977)(b) [e]	SP	WI	1.8	0.34	AC
12 months						
Females	Barker et al., 1994	SP, SU	SP	8.4	0.14	CW
	Masterton, 1991	SU	SU	9.9	0,37	CW
	Pajoumand et al., 2012	WI	–	–	–	–
	Polazarevska et al., 2011	SU	–	–	–	–
	Preti and Miotto, 2000	–	SP	8.8	0.12	CW
	Yip and yang, 2004	SP	SP	8.2	0.22	CW
	Zakharov et al., 2013	SP	–	–	–	–
Males	Barker et al., 1994	–	–	–	–	–
	Masterton, 1991	–	–	–	–	–
	Pajoumand et al., 2012	SP	SP	7.7	0.35	CW
	Polazarevska et al., 2011	SU	–	–	–	–
	Preti and Miotto, 2000	SP	SP	8.4	0.14	CW
	Yip and yang, 2004	–	SU	9.2	0.13	CW
	Zakharov et al., 2013	SP	–	–	–	–
Not evaluated by sex	Elisei et al., 2012	WI	–	–	–	–
	Geltzer et al., 2000	SP	–	–	–	–
	Minnaar et al., 1980	SU	SU	9.8	0.38	CW

Seasons: AU–Autumn, WI–Winter, SP–Spring, SU–Summer.
Classification of seasons:

[a] Acrophase value: 4 seasons (0-Autumn, 1-Winter, 2-Spring, 3-Summer) OR 12 months (0 to 2-Autumn,3–5-Winter,6–8-Spring,9–11-Summer).
[b] Method with significance in statistical analysis: AC-Cosinor by Acrophase, CW–Cosinor-Fourier by CircWave.
[c] Calendrical,
[d] Astronomic,
[e] Not indicated which was used.

articles (Akbaba et al., 2007; Al-Ansari et al. 1997; Santana Cabrera et al., 2010; Doganay et al., 2003; Hatzitolios et al., 2001; Islambulchilar et al., 2009; Seydaoglu et al., 2005; Tufekci et al., 2004) restricted of four seasons also showed acrophase in late spring (Fig. 3B). Only two articles (Santana Cabrera et al., 2010; Doganay et al., 2003) discriminated the data by sex, showing similar pattern for both male and female. We also describe the amplitude values, generated from fold change data, in figures and tables. The amplitudes were variable; however, we did not find any evident pattern comparing the studies (data not shown).

4. Discussion

The current review included mostly retrospective cross-section studies published in the last four decades and investigating the seasonal pattern of suicide attempts. The majority (23/29) reported a higher peak in suicide attempts in spring or summer. Only three articles did not find seasonality in suicide attempts (Aydin et al., 2013; Nakamura et al., 1994; Saadat, 2005). However, the study of Saadat (2005) was restricted to evaluate self-inflicted injuries from burns and the sample size was the lowest among the reviewed articles, which could have had an impact on the statistical analysis.

In a statistical approach using specific methods for data with rhythmic variation, we identified herein an overall seasonal pattern suggesting a peak in mid-late spring, considering articles individually or grouped. This result is similar to the findings observed in completed suicides (Christodoulou et al., 2012). The acrophases (near 9.0 for monthly data and 3.0 for season data) observed in individual studies indicate an early summer peak, which is close to the general tendency. In despite of the suggested differences between sexes in seasonality of suicide attempts previously reported, we did not find any pattern indicating that such differences occur, either in which was reported by authors or in our statistical analysis. The consistency of this epidemiological

Table 4
Seasonal variation of suicide attempts by violent and non-violent methods analyzed by rhythmic methods. Data arranged by months or seasons.

Studies	SEX	Season or month	Peak reported	Rhythmic analysis			
				Season	Acroph[a]	Amplitude	Method[b]
Non-violent							
Yip and yang, 2004	NE	M	SP/SU	SP	8.9	0.14	CW
Doganay et al., 2003	F	S	SU	–	–	–	–
Preti and Miotto, 2000	F	S	–	–	–	–	–
Doganay et al., 2003	M	S	SU	SP	2.7	1.25	AC
Preti and Miotto, 2000	M	M	WI	–	–	–	–
Violent							
Yip and yang, 2004	NE	M	SP	–	–	–	–
Doganay et al., 2003	F	S	–	SP	2.6	0.37	AC
Preti and Miotto, 2000	F	M	–	SU	9.3	0.11	CW
Doganay et al., 2003	M	S	SP/SU	SP	2.9	0.91	AC
Preti and Miotto, 2000	M	M	SP	SP	8.8	0.16	CW

[a] Acrophase value: M: Month (0–2-Autumn, 3–5-Winter, 6–8-Spring, 9–11-Summer) OR S: Meason (0-Autumn, 1-Winter, 2-Spring, 3-Summer).
[b] Method with significance in statistical analysis: AC-Cosinor by Acrophase, CW–Cosinor-Fourier by CircWave.

observation suggests that suicide behavior is strongly modulated by endogenous and/or environmental factors with seasonal variation.

Some studies reported a lower incidence (nadir) of suicide attempts in December (northern hemisphere) (Akbaba et al., 2007; Masterton, 1991). This might be explained by the greater impact Christmas exerts upon women. According to Masterton (1991), this event may produce an enhanced sense of belonging that could protect some women who are at risk of parasuicide. However, in this systematic review we reported 3 studies describing a higher incidence of suicide attempts in December (Elisei et al., 2012; Pajoumand et al., 2012; Wenz, 1977a). In our analysis, we identified a tendency for a late autumn/early winter in nadir.

There are evidences in literature suggesting that seasonality of completed suicide occurrence is dependent of violent methods (Maes et al., 1993). Massing and Angermeyer (1985), reported pronounced seasonality in suicides by hanging, but not seasonality in poisoning suicides (Massing and Angermeyer, 1985). A study based on quarterly data of suicides in Italy from 1984 to 1995 reported seasonal patterns only in suicides committed by violent methods (Preti and Miotto, 1998). Swiss data demonstrated that seasonal effects were found in hanging, jumping and drowning but not in other methods, whether violent or not violent (Ajdacic-Gross et al., 2003).

Only two reviewed studies discriminated the methods applied by sex in suicide attempts. They examined the methods clustering on violent and non-violent and found divergent results: among males, there was seasonality regardless of the method used. However, in females, only one study has identified seasonality in non-violent methods (Doganay et al., 2003). In our statistical analysis for rhythmicity, we identified seasonal variation in both methods, particularly in violent attempts, regardless of sex, with a peak mainly in spring. Interestingly, in two cases where there was no seasonal variation reported for females who attempted suicide through violent methods, seasonality was detected for the spring and early summer, respectively (Doganay et al., 2003; Preti and Miotto, 2000), suggesting that cosinor analysis may help better identify this variation.

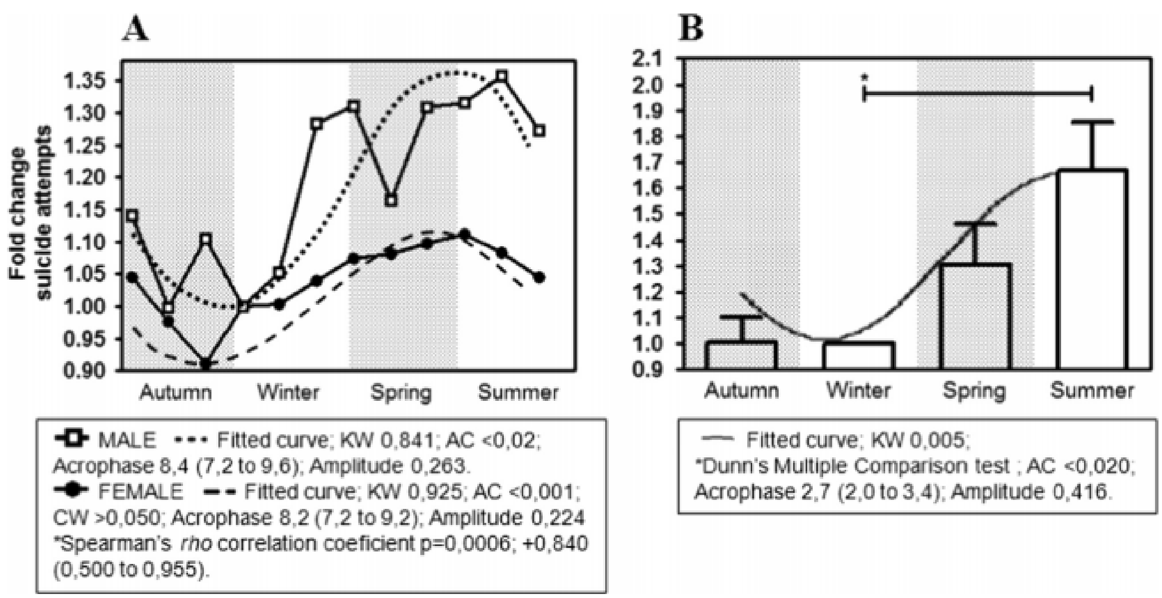

Fig. 3. Observed (bars and symbols) and estimated (fitted curve) distribution of suicide attempts among studies analyzed as a group and restricted by source (hospital) and method (self-poisoning). A–Monthly data of 4 articles separated by sex (Masterton, 1991; Pajoumand et al., 2012; Polazarevska et al., 2011; Yip and Yang, 2004). B–Seasonal distribution from 8 articles with data restricted to seasons (Akbaba et al., 2007; Al-Ansari et al., 1997; Santana Cabrera et al., 2010; Doganay et al., 2003; Hatzitolios et al., 2001; Islambulchilar et al., 2009; Seydaoglu et al., 2005; Tufekci et al., 2004). KW–Krukal Wallis test; AC–Acro; CW–Circwave. Acrophase value: Month (0–2-Autumn, 3–5-Winter, 6–8-Spring, 9–11-Summer) or Season (0-Autumn, 1-Winter, 2-Spring, 3-Summer). Bars plotted in mean with SEM. 95% confidence interval in round brackets.

Considering the great heterogeneity of the studies, we also restricted the statistical analysis to individuals who attempted suicide by self-poisoning, from data provided by hospital source and considering sex. The pattern observed was very similar to the general analysis, with a peak in late spring for both males and females. Although the heterogeneity between studies does not allow us to generalize results for all conditions with confidence, our findings for both sexes considering a non-violent method, in a more homogenous condition, which have the same pattern observed for completed suicide, may indicate that a higher incidence of suicidal behavior in spring is a universal phenomenon.

Another important risk factor for suicide behavior is psychiatric disorders with a seasonal profile (Geoffroy et al., 2014; Postolache et al., 2010; Yip et al., 2006). This contributes significantly to the seasonal variation of suicide attempts and it is not always possible to assess. Studies on Swedish database reported a spring peak of suicides in patients with alcohol addiction (Bradvik and Berglund, 2002), and an autumn peak in patients who had severe depression (Bradvik, 2002; Giner et al., 2013; Parra Uribe et al., 2013). Only seven reviewed articles discriminated the presence of psychiatric conditions in subjects that attempted suicide, without examining possible correlations with seasonality (Chien et al., 2013; Doganay et al., 2003; Elisei et al., 2012; Hatzitolios et al., 2001; Minnaar et al., 1980; Pajoumand et al., 2012; Valtonen et al., 2006).

Socioeconomic factors also could influence the seasonality of attempted and completed suicides. Some researches indicated that seasonal patterns of suicide rates are higher in rural areas compared to urban areas (Chew and McCleary, 1995; Maes et al., 1993; Micciolo et al., 1991). Micciolo et al. (1991) evaluated the seasonality of completed suicides in Italy (1969–1984) and found that peaks of suicide in spring were more notable in rural areas, although the suicide rates were higher in urban regions. In a review, Christodoulou et al. (2012) suggested that suicide patterns could be related to the intensity of seasonal activities such as agricultural work in the rural areas. In fact, a spring peak of suicide was relatively lower in industrial countries compared to agricultural countries (Chew and McCleary, 1995). In some cases, the peaks in the spring could be explained due to the availability of pesticides in agriculture, mostly during the crop-growing season (Muller et al., 2011). However, these socioeconomic variables were not evaluated in the seasonality of suicide attempts.

The biological mechanisms underlying seasonality in completed and attempted suicides are not yet known. Some hypotheses have been proposed to elucidate this phenomenon. One such explanation considers the climatic/meteorological factors influencing biological responses to the seasonal variations (Bando et al., 2009). These environmental factors could explain the previously described differences between rural and urban areas, with the influence, for example, of a strong *zeitgeber* in the former, as it has been observed (Carvalho et al., 2014).

Findings suggest that sunshine-regulated hormones, such as serotonin, melatonin and vitamin D, may have a role in triggering suicide (Fountoulakis et al., 2001; Grudet et al., 2014; Nagy et al., 2015; Petridou et al., 2002; Sher, 2006; Umhau et al., 2013; Vyssoki et al., 2012). If it is true, one would expect to observe a more pronounced seasonal variation in suicide risk with increasing distance from the Equator. In fact, studies involving completed suicides have demonstrated that the proximity to the equatorial region may diminish the effect of seasonality in suicide rates (Benedito-Silva et al., 2007; Cantor et al., 2000; Heerlein et al., 2006; Parker et al., 2001). The most plausible explanation for this phenomenon is that seasonal changes in sunlight exposure and the duration of the day vary with latitude. These seasonal asymmetries should be different at distinct latitudes of one hemisphere, but similar for both hemispheres. The photoperiod and seasonal changes are less evident near equatorial region (Heerlein et al., 2006).

In a cross-sectional data from 28 countries, Chew and McCleary (1995), found a peak of suicides in spring. However, only populations in the temperate zone exhibited suicide seasonality, suggesting an influence of geographical latitude. In our study, the majority of the researches reviewed in suicide attempts was performed on countries localized in northern hemisphere and only two in the southern hemisphere, all distant (at least 20°) from the Equator line (where seasonal climatic variations are less noticeable). From 28 countries analyzed by Chew and McCleary (1995), nine were present in our study. From these, five (Australia, England, Italy, Scotland and South Africa) presented the same seasonal profile, two presented different pattern (USA in winter and Germany in summer), one did not show seasonality (Greece), and one could not be analyzed due to data disposal (Finland).

An overall pattern for a peak of suicide attempts in mid-late spring was observed independent of country. It was not possible to consider seasonal classification in our study due to lack of information. If an astronomical calendar is used, which takes into account the photoperiod variation, the observed acrophase would be represented earlier compared to calendrical classification. Hence, the type of seasonal classification could leads to different interpretations of this seasonality and should be considered in future studies.

Knowledge regarding the time when people attempt suicide allows the government, the public health system and professionals to create prevention strategies, and strengthen emergency units to provide assistance to affected people.

4.1. Limitations

Our analysis shows an overview of data worldwide which can help understand that seasonality of suicide attempts would be a general fact. However, the study was conducted by grouping very diverse populations: different ages (adolescents, adults), specific groups by method (poisoning, burn), ethnic groups with different social, economic and cultural conditions in different countries, as well as the source of obtaining data (cases that reach the health system are probably more severe than those that remain concealed from official statistics). All this diversity could lead to a general conclusion unrefined. Unfortunately, we did not find many studies discriminating suicide attempts according to methods, clinical samples or age in the context of seasonality, which could lead to a more refined analysis. We tried to address this question by restricting the analysis to sex, type of method and source of data, which leads to the same observed pattern.

The insertion of secondary data in the cosinor formulae, presented as means, instead of the individual original data, can trim down the natural variance leading to an artificially increased significance. However, when researchers are unable to perform longitudinal sampling because of methodological limitations, the accumulated temporal distribution of data can be accomplished. So an educed monthly rhythm of suicide attempts can be produced when populational data are accumulated over many years (Refinetti et al., 2007). The use of Cosinor method for determining the individual oscillation profile (only one series, ie without repetitions) has also been accomplished too. There are several examples in the literature using Cosinor to the determination of oscillations in serum measurements and gene expression without the necessity of repetitions (Figueredo Dde et al., 2013; Hida et al., 2009; Kavcic et al., 2011).

Other potential limitations from our study also include loss of information from articles that could not be accessed, restricted regions evaluated without data in countries near equator line, other variables not evaluated such as age and psychiatry disorders, and inability to identify other possible rhythmic variation patterns in the sample using the proposed methods.

5. Conclusion

We described in this systematic review that seasonal variation is an important epidemiological observation also for suicide attempts. To our knowledge this is the first systematic review on this topic. An overall pattern was observed for a peak in spring, independent of sex, region and type of method used. This tendency for a higher incidence of suicide behavior in spring could be a consequence of the increasing photoperiod and light intensity in this season. However, further studies are necessary to confirm this hypothesis and elucidate its neurobiological basis, with potential clinical and therapeutic repercussions. A proposed design for future researches on the seasonality of suicide attempts may consider the following factors: a significant sample size in several countries of different latitudes, photoperiod variation, sex, methods used, the influence of psychiatric disorders and the use of specific tests for the analysis of data with rhythmic variation.

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CAPITULO 2

“**Seasonal Variation of Suicides in Brazil: Evidences for a Latitude Effect”**

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SEASONAL VARIATION OF SUICIDES IN BRAZIL: EVIDENCES FOR A LATITUDE EFFECT

ABSTRACT

Seasonal variation in suicides have been reported in several countries, with peak in late spring/early summer. There is some evidence that seasonality is related to latitude. The evaluation of these parameters in a country with a large territorial extension, under the same aspect of case registration and analysis, could bring more conclusive evidences. **Methods:** This study was designed to evaluate the influence of latitude on the seasonality of suicide rates in Brazil in the period of 2010 to 2015, since it is a country with large territorial extension (including tropical and temperate zones), ranging from +5°26' to -33°74' latitude. Monthly data from external causes of mortality (X60-X84, ICD-10) by city were collected from Brazilian Ministry of Health. Seasonal effect and day length in latitude groups were evaluated by correlations and rhythmic analysis. **Results:** A total of 61.824 suicides were reported from 5.045 cities. Suicide rate and amplitude exhibited higher values in regions farther distant from the Equator line, in individual data by city and grouped by latitude. A seasonal pattern with peak in December (summer solstice) and nadir in June (winter solstice) was found. This seasonal pattern were not observed in latitude bands near the Equator line, and becomes evident only when descending the latitude (-15º and below). Grouping cities at every 5 degrees showed an increase in suicide rates and the presence of seasonal variation with the same oscillatory pattern of photoperiod variation in lower latitudes. The rhythmic pattern in suicide was strongly correlated to photoperiod variation in these groups. **Limitations:** Socio-demographic data, individual major events and subgroups by suicide methods were not taken into account. Temperature data of the study period for all cities were not included in the analysis since this information was not available. Underreporting of suicide cases is a possible problem around the world. **Conclusion:** These data highlight the environmental effect of latitude, suggesting that photoperiod could be related to the seasonality of suicidal behavior.

Key-Words: Seasonality, Suicide, Latitude, Photoperiod, Peak/Trough ratio, Brazil.

INTRODUCTION

Suicide is a serious public health problem worldwide. Each year, around 800.000 people complete suicide and even more people try to commit suicide. Each suicide is a tragedy that affects families, communities and entire countries and has lasting effects on the society. The World Health Organization has suicide prevention as high priority (World Health Organization 2014).

Many countries have reported a seasonal occurrence in suicidal behavior. In both southern and northern hemispheres, the frequency of suicides increases in the period between late spring and early summer (Christodoulou *et al.*, 2012; Rocchi *et al.*, 2007; Cabrera *et al.*, 2010; Coimbra *et al.*, 2016). A cross-sectional study in 28 countries showed a high prevalence of suicides in the spring (Chew and McCleary 1995).

Although some studies indicate differences between individuals who commit suicide of those who attempt suicide, a similar pattern of oscillation with incidence in spring / summer has also been reported in suicide attempts (Yip and Yang 2004; Coimbra *et al.*, 2016). Despite the importance of the cultural, social and economic aspects that influence suicidal behavior, the seasonal occurrence cannot be explained only by these factors.

Circannual rhythms are widely distributed in plants and animals, and there are many evidences showing that humans also present seasonal variations in physiology and behavior. A widespread seasonal gene expression has revealed annual differences in human immunity and physiology (Dopico *et al.*, 2015). A total of 23% of the protein-coding genome were identified as having seasonal variation in expression with 2.311 mRNAs defined as summer genes and 2.826 winter genes, related to risk biomarkers for cardiovascular, psychiatric and autoimmune diseases (Dopico *et al.*, 2015). Seasonal changes in brain monoamine systems, such as dopamine (Nieoullon 2002; Eisenberg *et al.*, 2010; Karson *et al.*, 1984), serotonin and its metabolites (Kanikowska *et al.*, 2009; Brewerton *et al.*, 2018), brain serotonin transporter (Praschak-Rieder *et al.*, 2008; Ruhé *et al.*, 2009) and neurotrophins (Molendijk *et al.*, 2012) have also been reported.

The seasonal variation in molecules and hormones leads to changes in mood and behavior, as well described in winter depression of the Seasonal Affective Disorder (Wirz-Justice 2018). Several other symptoms and diseases have a seasonal oscillatory profile, such as angina pectoris, hypertension, high cholesterol levels, diabetes, joint diseases and psychological illnesses, peak episodes of bipolar disorder mania in spring/summer and others (Wirz-Justice 2018; Basnet *et al.*, 2016; Øyane *et al.*, 2010; Bedrosian and Nelson 2017; Young and Dulcis 2015; Geoffroy *et al.*, 2014). Evaluations by imaging methods indicate seasonal variations in activity and volume of different brain regions, including healthy people (Meyer *et al.*, 2016; Miller *et al.*, 2015).

The main clue to entrain the endogenous rhythms of plants and animals to a cyclical environment is the light (Bedrosian and Nelson 2017; LeGates, Fernandez, and Hattar 2014). Therefore, the annual cycle of photoperiod of the seasons is the most important synchronizer of circannual rhythms, and this environmental modulation of the circadian rhythm may lead to seasonal suicidal behaviors in individuals with vulnerability (Wirz-Justice 2018).

The circadian photoperiod manipulation is sufficient to simulate physiological changes in animals, as it occurs in seasons (Seco-Rovira *et al.*, 2015; Jastroch *et al.*, 2016). Other researches demonstrated the effect of photoperiod affecting behavior and gene expression (Leach *et al.*, 2013; Otsuka *et al.*, 2014; Goda *et al.*, 2015; Green *et al.*, 2015; Nagy *et al.*, 2014; Dellapolla *et al.*, 2017) and a large molecular disarrangement between brain and body tissues (Evans *et al.*, 2013, 2015; Leach *et al.*, 2013; Yoshikawa *et al.*, 2017; Oquendo *et al.*, 2014).

Among environmental factors, sunlight and temperature have been most often associated with the seasonality of suicide (Woo, Okusaga, and Postolache 2012; White *et al.*, 2015; Vyssoki *et al.*, 2014). Considering that light is the main environmental clue for circadian rhythm synchronization, and the photoperiod plays an important role in animal physiology, therefore, humans must also be influenced by the variation of photoperiod that occurs in the seasons. Seasonal influences are particularly marked at extreme latitudes, where variations in external conditions are most pronounced.

In this work, we investigated the influence of latitude on the seasonality of suicides. Since Brazil is a country with a large territorial extension (including tropical and temperate zones), ranging from +5°26’ to -33°74’ latitude and -34°82’ to -73°97’ longitude, it is possible to analyze more accurately the effect of the seasonality of suicide over several areas, within the same notification system.

MATERIALS AND METHODS

On the DATASUS website (http://www2.datasus.gov.br/DATASUS/index.php) of the Brazilian Ministry of Health, in the System of Mortality Information, monthly data from 2010 to 2015, in external causes of mortality were collected using the intentional self-harm (X60-X84) of the International Classification of Diaseases - 10 (ICD-10) category by city. The population, demographic density, latitude and longitude of each city were determined by the demographic census of 2010 through the Brazilian Institute of Geography and Statistics. Photoperiod data by latitude were collected based on the National Institute of Meteorology (Varejão-Silva 2016). This is an ecological study with time series.

Graphics and analyzes were performed using the GraphPad Prism v7.0, IBM SPSS v*20*, Microsoft Excel 2013, CircWave v1.4 (http://www.euclock.org/results/item/circ-wave.html), TabWin v3.6b, Cosinor v1.0 (http://www.circadian.org) and MetaCycle (https://cran.r-project.org/web/packages/MetaCycle/index.html).

To investigate oscillatory patterns in suicide occurrences and calculate rhythmic parameters (acrophase, amplitude and mesor), we used the cosinor regression test adjusted for a fixed 12-month period (Refinetti, Cornélissen, and Halberg 2007). CircWave produced a Fourier-curve improving the data description by adding as many harmonics to the wave fit as the data allow.

MetaCycle is an R package and has the function Meta2d that incorporates ARSER, JTK_CYCLE and Lomb-Scargle to detect rhythmic signals from time-series datasets (Wu *et al.*, 2016). The Meta2d uses the q-value as statistical significance and also output a relative amplitude value (rAMP) as the ratio between amplitude and baseline.

Heat maps were made in Excel, using the conditional formatting function of the color scale. The exact location of cities and suicide rates on Brazil map were done in TabWin software.

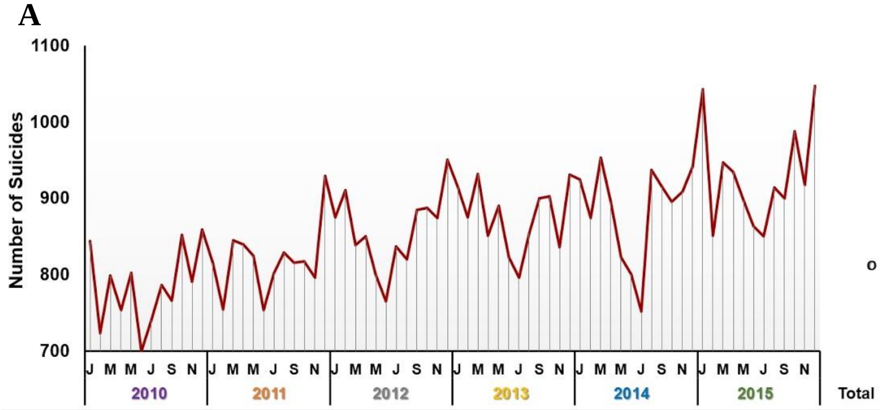
Peak/Trough (P/T) ratio of suicide rates were performed to give an amplitude-like estimation in time series without significant rhythmicity detected by usual methods. To perform P/T analyses, suicide rates data were transformed into square root +1 to avoid zero values. We used Spearman correlation coefficient (Rho) to investigate possible associations between latitude, P/T, amplitude and suicide rate.

The latitudes from suicide rate data grouped in 1 degree of latitude were worked as modules (without the presence of positive or negative signals) to evidence the effect of distancing from the

Equator line (latitude 0°). The mean of the 5 degree latitude groups were analyzed by ANOVA with Tukey's multiple comparisons test and significance of $p<0.05$.

RESULTS

In the period from 2010 to 2015, a total of 61.824 suicide deaths were reported from 5.045 cities in Brazil. Considering the last census (2010), the population of Brazil was 190.732.694 people and the suicide rate for the year 2015 was 5.8 cases per 100.000 inhabitants. Despite an increase of 18.4% in suicide deaths comparing the first and the last year of the report (Figure 1A), the general behavior of suicides in Brazil considering the period analyzed, indicated a seasonal pattern with a peak in December (summer solstice) and nadir in June (winter solstice) (Figure 1B).



	2010	2011	2012	2013	2014	2015	Total
Cities	2.703	2.765	2.803	2.886	2.848	2.994	5.045
Suicides	9.420	9.824	10.295	10.507	10.623	11.155	61.824

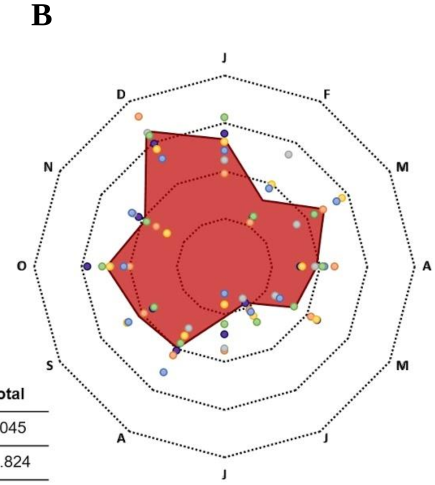


Figure 1. Seasonal variation of suicide occurrences in Brazil from 2010 to 2015. A - Occurrences over the year and number of cities reported. B - Polar Plot of suicide cases with seasonal peak in December and nadir in June/July. Acrophase in December (Summer solstice) and nadir in June (Winter solstice), Mesor =858.7 and Relative Amplitude =0.051.

When suicide occurrences were separated by degrees of latitude, the seasonality of the suicide becomes evident when descending the latitude (Figure 2 and 3). The northern region of Brazil, despite having the largest territorial extension, is the one with least cities reporting suicides during this period. The seasonal pattern of occurrences is not observed in latitude bands near the Equator line (North and Northeast regions of the country) (Figure 3A,B). Lower latitudes also have a higher rate of suicides. The city with the highest suicide rate was Passo Fundo (-28°23' latitude) in Rio Grande do Sul, with a mean of 313.5 suicides per year in 100.000 inhabitants, totaling 138 cases in 6 years.

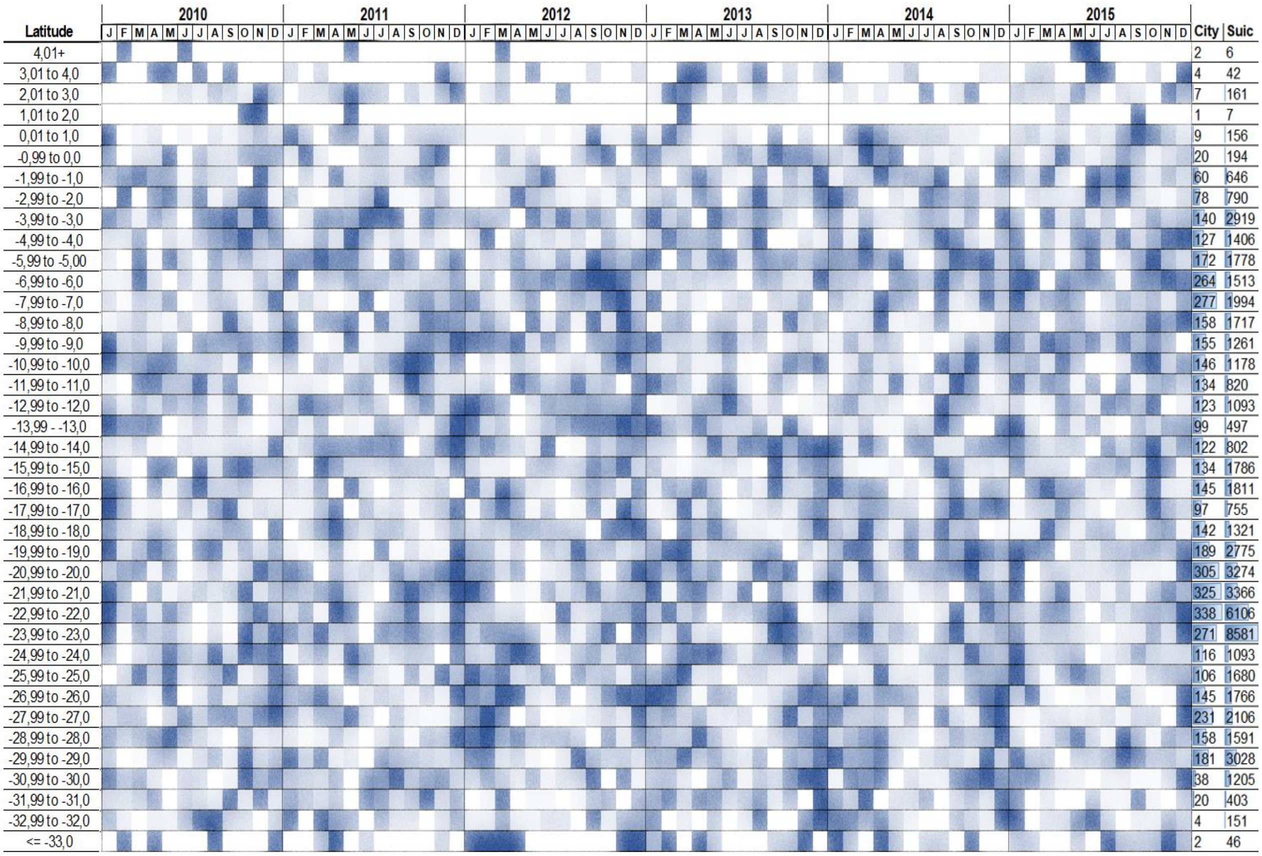


Figure 2. Distribution of suicides in Brazil by year/month. A heatmap of suicides reported per month over the period study (2010-2015). Cities were grouped each 1 degree of latitude. Squares ranging from white to blue indicates low to high suicide occurrences during the year. Whitish areas are evident in winter months (middle years). City – total number of cities reporting suicide. Suic – total number of suicides in the period study.

Most of the Brazilian cities are located in the southern hemisphere. Only 23 (0.46%) of the total of 5.045 reporting cities are above the Equator line. In order to evaluate the effect of latitude on the suicide rate in the hemispheres (latitude vs suicide rate in the northern hemisphere, Rho +0.170 $p=0.438$; and southern, Rho -0.283 $p<0.0001$ - data not shown), the distancing from the Equator line (latitude 0°) in relation to the suicide rate was evaluated. There was a significant correlation despite not being strong (Rho +0.281 $p<0.001$), indicating that the further away from the Equator line, the higher the suicide rate (Figure 4A). A weak but significant correlation (Rho +0.253 $p<0.001$) was observed between peak/trough ratio (an amplitude estimation) and the distance from the Equator line (Figure 4B), also indicating an increase in the amplitude of the rhythm in latitudes far from the equatorial line.

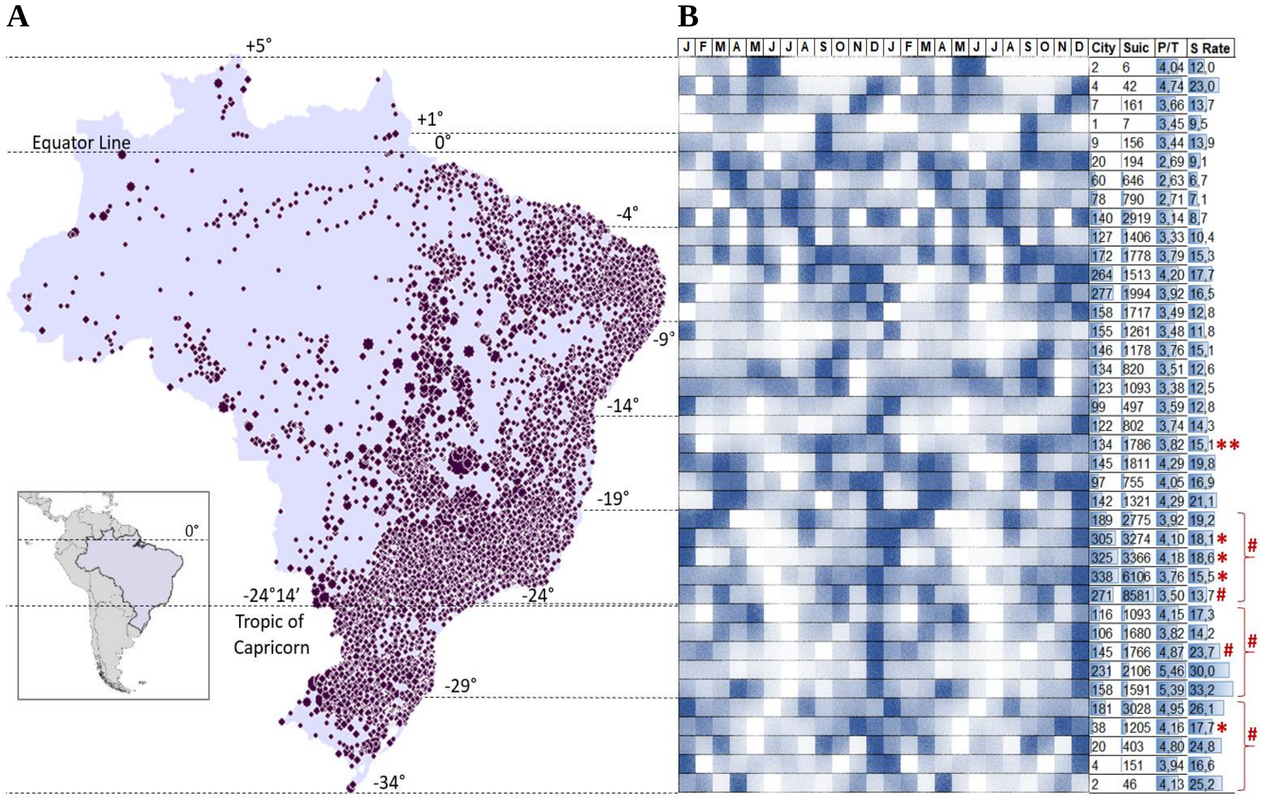


Figure 3. Distribution of suicides in Brazil by month (2010-2015). **A**- Map of suicide rates in cities by latitude. The highest suicide rate was in Passo Fundo (-28°23' latitude) with mean of 313.5 suicides per 100.000 inhabitants/year (not visible in the map – it is overlapped). **B**– A summary doubleplotted heatmap of suicides distributed per month. The whitish area in the winter and dark blue in the summer become even more evident as the latitude decreases. Analysis of seasonal rhythmicity with a significant difference in *p-value<0.05, **p-value<0.01 and #p-value and q-value<0.001. Red keys indicate analysis at every 5 degrees of latitude. City – total number of cities reporting suicide. Suic – total number of suicides in the period study. P/T – Peak/Trough ratio. SRate – mean suicide rate in 100.000/inhabitants per year.

In order to increase data volume, and thus evaluate the seasonality of suicides, cities were assessed every 1 degree of latitude. Both suicide rate (Rho +0.729 p<0.0001) and peak/trough ratio (Rho +0.687 p<0.0001) correlate positively to increased latitude (Figure 4C and D).

The analysis of the seasonality of suicide occurrences, grouping cities at every 5 degrees of latitude, indicated that lower latitudes exhibited higher suicide rates (Figure 5) and seasonal variation with high occurrence (acrophase) in December (-19°00' to -23°99' and -29°00' a -33°99') and January (-24°00' to -28°99') (Figure 6). The nadir of the cycle occurs in June, with the exception of the group -24°00' to -28°99' which is in July. This seasonal cycle oscillates in the same pattern of the photoperiod variation (cross-correlation lag 0.0 in the 3 latitude ranges).

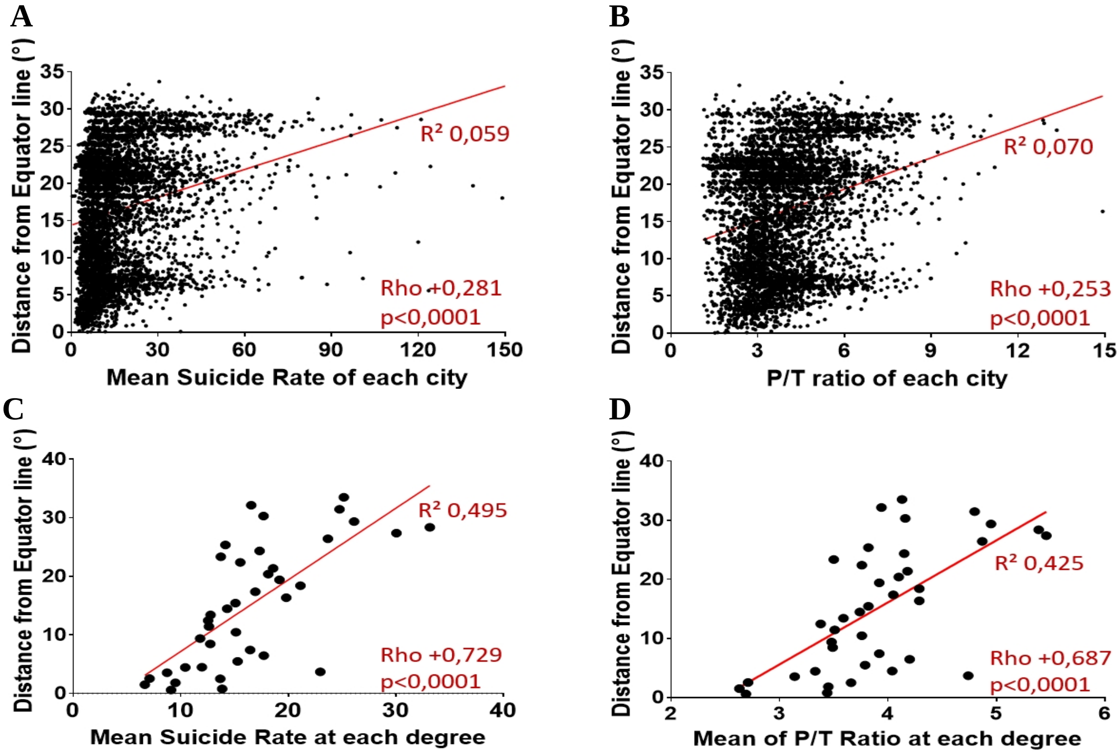


Figure 4. Evaluation of the mean suicide rates per year (A) and Peak/Trough ratio (B) of each city observed by the distance from Equator line (0º latitude). Five data points are outside the axis limits (A) because they have a high suicide rate. Mean of suicide rate (C) and P/T ratio (D) at every 1 degree of latitude. The P/T ratio gives an estimate of the amplitude of the rhythm. Suicide rates data were transformed into square root +1 to avoid zero values (C, D). Latitudes were treated as modules only to evidence the effect of the equator line distance. Spearman correlation Rho.

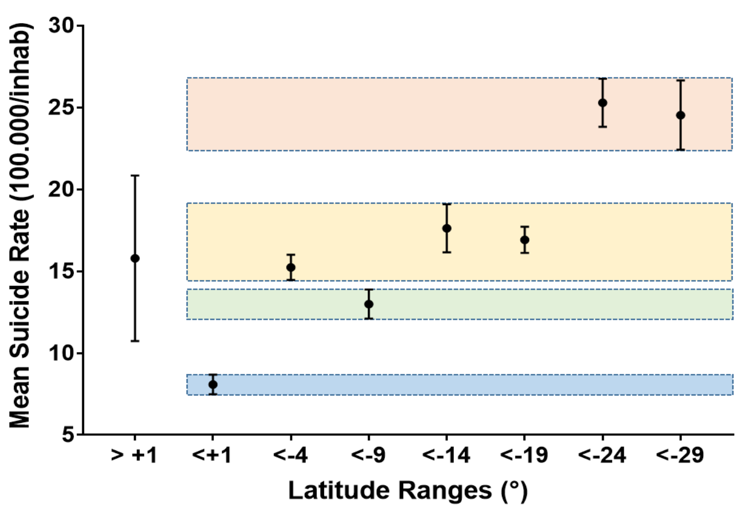


Figure 5. Suicide rate of cities grouped at every 5 degrees of latitude. Bars grouped within the same rectangle (same color) showed no significant difference between them. Significant difference was observed between groups of different color (p<0.05). Bars in mean with 95% confidence interval. ANOVA F(7.5037) = 60.7 (p<0.0001) with Tukey's multiple comparisons test.

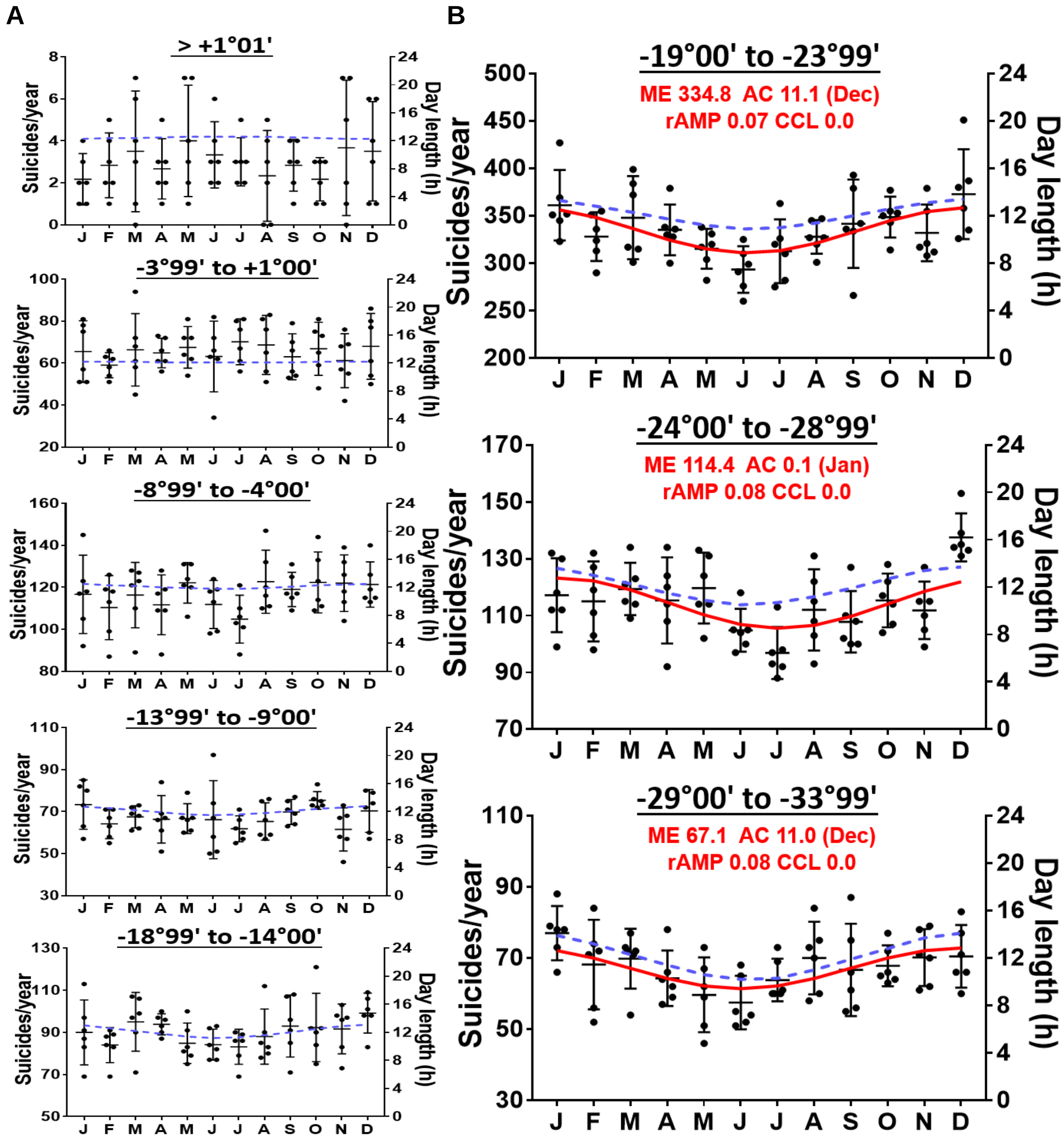


Figure 6. Seasonality profile of suicides grouped by cities at every 5 degrees of latitude. Analysis of the rhythm profile of latitude bands by month by year. **A-** Cities close to the equatorial line, grouped every 5 degrees to latitude -18°99' did not exhibit seasonality. **B-** Seasonality of suicide occurrences detected in cities below -19° latitude and correlation with seasonal variation of photoperiod. Cross-correlation between the fitted curve by Fourier (red line) and the photoperiod curve (blue dashed line). ME – Mesor, AC – Acrophase, rAMP – Relative Amplitude, CCL – Cross-Correlation Lag.

DISCUSSION

In this work, we evaluated 61.824 reported cases of suicide to investigate the relationship between latitude and seasonality. Our study has shown a serious concern about the increase in suicide occurrences over the years and has confirmed the seasonal profile of completed suicides, with peak in late spring / early summer and nadir in winter.

In accordance with previous studies, we demonstrated that the seasonality of suicide is directly related to latitude. However, in our study, it was possible to evaluate two conditions (near and far from the Equator line) at the same time/country and confirm the hypothesis of the relationship between latitude and seasonality. In countries near the Equator line, as Colombia, Panama, Venezuela and Singapura, no evidence has been found of seasonal variation in suicidal behavior (Parker, Gao, and Machin 2001; Sánchez, Tejada, and Martínez 2005; Chew and McCleary 1995). However, in countries farther from latitude 0°, there is an oscillation in suicide occurrences along the year, showing the same pattern of higher frequency in late spring/early summer and lower frequency in winter, independent of the hemisphere (Björkstén, Kripke, and Bjerregaard 2009; Davis and Lowell 2002; Dixon and Kalkstein 2018; Tsai and Cho 2012; Santurtún, Santurtún, and Zarrabeitia 2017; Jee *et al.*, 2017).

The seasonality was identified only after 15 degrees of distance from the equatorial line in cities grouped at each 1 degree of latitude, and after 19 degrees of distance when grouped at every 5 degrees. Our study corroborates with other findings also identifying seasonality in countries from these latitude ranges: in 9 USA counties ranging from 25ºN to 47ºN (Dixon and Kalkstein 2018), Taiwan in 23°N (Tsai and Cho 2012), Mexico in 23ºN (Fernández-Niño *et al.*, 2016), Japan in 33ºN (Petridou *et al.*, 2002), South Korea in 35ºN (Jee *et al.*, 2017), Greece in 38ºN (Petridou *et al.*, 2002), Turkey in 38ºN (Akkaya-Kalayci *et al.*, 2017), Spain in 40ºN (Petridou *et al.*, 2002; Santurtún, Santurtún, and Zarrabeitia 2017), Australia in 29°S (Petridou *et al.*, 2002; Cantor, Hickey, and De Leo 2000), Chile in regions from central north 30ºS to central south 43ºS (Heerlein, Valeria, and Medina 2006), South Africa in 35ºS (Flisher *et al.*, 1997).

In the lowest degrees of latitude of the country, no seasonality was found and it is probably due to the very small number of cases. However, when these data were grouped, it was possible to identify an evident seasonal profile. Heerlein, Valeria, and Medina (2006) splitted data from Chile in 4 latitude zones with a total of 5.460 cases of suicide. The northern (latitude 17º to 30º) and southern (43° to 56°) zones did not show seasonality. This was attributed also to the small number of cases (5.3% and 2% of the total suicides, respectively).

In another study in Brazil, Benedito-Silva, Pires, and Calil (2007) evaluated the seasonality of suicides in 31.228 cases registered in 8 Brazilian states (3 from the North / Northeast, 2 in Southeast and 3 South) from 1979 to 1990. A significant spring/early summer peak of suicide were also found. In the present study, all Brazilian cities that reported suicide (5.045 cases) in 6 years of study were analyzed. Grouping cities by latitude allowed a more accurate analysis covering the entire country, something that could not be possible to identify otherwise.

There is a great diversity of statistical analysis to identify seasonality being used in different studies/countries, which can, in some conditions, generate confusing interpretations. Distributed lag nonlinear modeling (Dixon and Kalkstein 2018), cosinor analysis (Bando and Volpe 2014; Benedito-Silva, Pires, and Calil 2007), Box-Jenkins methodology (Sánchez, Tejada, and Martínez 2005), a proportionate reduction in error formula (Chew and McCleary 1995), ARIMA/SARIMA regression models (Tsai and Cho 2012), ANOVA (Tsai and Cho 2012; Santurtún, Santurtún, and Zarrabeitia 2017), spectral decomposition and wavelet analysis (Fernández-Niño *et al.*, 2016), chi-squared analysis (Cantor, Hickey, and De Leo 2000; Sumarokov *et al.*, 2015). In our study, the comparison of the data both near and far from the Equator line was performed using the same rhythmic analysis method. Another advantage was the use of the same registration system that is unified for reporting cases of suicides in Brazil. Being from the same country, the comparison between states/cities becomes easier and more reliable.

Evidences that latitude is directly related to suicide rates were found in Brazilian suicide data. There was an increase in suicide rates in the southern latitudes of the country, as the latitude decreases. Studies in Chile (Heerlein, Valeria, and Medina 2006) and Greenland (Björkstén, Kripke, and Bjerregaard 2009) also identified this profile of increased suicide rate. Davis and Lowell (2002) analyzed the variation in suicide rates and geographic latitude, and found a positive linear relation.

The findings in Brazil regarding amplitude were also interesting. As it distances itself from the Equator line, the suicide rate and amplitude of suicides tend to increase. Benedito-Silva, Pires, and Calil (2007) also found a relationship between amplitude and latitude, in states with higher rates of suicide. Rocchi *et al.*, (2007) in Italy, indicated the positively relationship between amplitude and suicide rate, so that as the suicide rate increases, the seasonal amplitude also rises.

The causal mechanism for this seasonal pattern is unknown. Day length (photoperiod) is a probable modulator of the circannual rhythmicity of suicides due to its relation to the circadian rhythm, in the adjustment of the light-dark cycles. Others studies suggested this association with sunlight duration, however only with the annual rhythm of violent suicides (Vyssoki *et al.*, 2012, 2014; Lambert *et al.*, 2003; Preti and Miotto 1998; Maes *et al.*, 1994).

It is well established that many biological processes are under circadian control and the timing of light exposure affects mood and brain circuits (Bedrosian and Nelson 2017). Light therapy has been used successfully to treat or reduce the symptoms of a variety of mood disorders in humans, including bipolar disorder, major depression, seasonal depression, postpartum depression (Pail *et al.*, 2011; Lam *et al.*, 2016; Dallaspezia, Suzuki, and Benedetti 2015; Phelps 2017). In fact, not only light has its importance, but the alternation between light:dark cycles which defines the photoperiod. Dark therapy has been recently explored to treat symptoms of bipolar disorder (Phelps 2017). Several diseases have been associated with disruptions of the circadian rhythms, including bipolar disorder, seasonal affective disorder, Alzheimer, Parkinson, and others (Nováková *et al.*, 2015; Wirz-Justice 2018; Bedrosian and Nelson 2017; Homolak *et al.*, 2018; Wang *et al.*, 2018), all suffering, therefore, seasonal influences.

In animals, exposure to different photoperiod regimes leads to changes on biological rhythms and mood behavioral (LeGates, Fernandez, and Hattar 2014; Dellapolla *et al.*, 2017; Xu *et al.*, 2016). In recognizably seasonal animals, the photoperiod adjustment is sufficient to simulate the physiological changes present in the seasons, as occurs in hamsters that have their reproductive function modified when submitted to a short photoperiod protocol (Seco-Rovira *et al.*, 2015; Jastroch *et al.*, 2016). In non-considered seasonal rodents, when exposed to different photoperiod regimes, they present behavioral and physiological changes in circadian rhythmicity (Leach *et al.*, 2013; Otsuka *et al.*, 2014; Goda *et al.*, 2015; Green *et al.*, 2015; Nagy *et al.*, 2014; Dellapolla *et al.*, 2017). Experiments in several rodents indicate a depression-like behavior, in both diurnal and nocturnal rodents, similar to human depression when submitted to a short photoperiod (Krivisky *et al.*, 2011; Leach *et al.*, 2013; Otsuka *et al.*, 2014; Xu *et al.*, 2016). Dellapolla *et al.*, (2017) demonstrated that long days enhanced long-term recognition memory and altered hippocampal clock function in mice.

In long photoperiod, a large molecular disarrangement with decoupling between brain structures were found, including brain areas potentially related to human suicide (Evans *et al.*, 2013, 2015; Leach *et al.*, 2013; Yoshikawa *et al.*, 2017; Oquendo *et al.*, 2014). Evans *et al.*, (2015) showed that Shell neurons, a functional compartment of the suprachiasmatic nucleus (SCN), when in long days, coordinate the phase and amplitude of tissue clocks throughout the brain and body (total of 17 different tissues examined), acting decoupled from the Core SCN, the other functional compartment. Yoshikawa *et al.*, (2017) using bioluminescence images of luciferase reporters in SCN slices of mice exposed to a long or short day, identified at least three oscillating regions possibly related to the photoperiodic response and transfer of seasonal information to physiology and behavior. This disarrangement in gene expression in brain areas, which may result in mood alterations, associated with other important environmental cues, such the external temperature (Yadlapalli *et al.*, 2018; Machado *et al.*, 2018; Kim *et al.*, 2016; Tsai and Cho 2012) may aid in the predisposition to seasonal suicidal behavior.

As previously discussed, some evidences point to photoperiod as the possible modulator of the seasonality of suicidal behavior: light is the main environmental cue to entrain the internal clock to the external environmental rhythms; animals subjected to photoperiod regimes (simulating seasons) develop molecular and behavioral changes in the biological rhythmicity; exposure to light has been used in the treatment of some human diseases, including seasonal affective disorders; the seasonality of suicide has been related only to latitudes where the environmental effect of the seasons are more striking. Despite these observations, we cannot rule out the influence of other important variable such as temperature, which has also been widely described (Maes *et al.*, 1994; Tsai and Cho 2012; Akkaya-Kalayci *et al.*, 2017; Kim *et al.*, 2016; Likhvar, Honda, and Ono 2011). Dixon and Kalkstein (2018) have suggested that this lack of consistency to link environmental conditions with suicide rates is possibly a result of differing geographic locations, variables and methodologies. Unfortunately, the cities included in the study period did not have temperature data available for analysis.

This study highlights the environmental effect of latitude, suggesting that photoperiod may be related to the seasonality of suicides, and shows the need to better understand the relationship between circadian rhythm modulators, seasonal environmental factors and suicidal behavior for an effective intervention in the seasonal incidence of suicide cases.

Limitations: Socio-demographic data, individual major events and subgroups by suicide methods were not taken into account. Temperature data of the study period for all cities were not included in the analysis since this information was not available. Underreporting of suicide cases is a possible problem around the world.

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CAPÍTULO 3

“**Increased photoperiod induces an antidepressant-like behavior and disrupted rhythmic expression of m*Per2* and m*Bdnf* in brain regions associated with suicide”**

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Increased photoperiod induces an antidepressant-like behavior and disrupted rhythmic expression of m*Per2* and m*Bdnf* in brain regions associated with suicide

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Running Head: Photoperiodic induction of antidepressant-like effect in mice

ABSTRACT

Objectives: Suicidal behavior presents a higher incidence during spring/summer according to worldwide epidemiological studies. The same seasonal pattern has been associated with mania symptoms of bipolar disorder (BD). These may be related to the modulatory effect of the increased photoperiod on circadian rhythms. However, the biological basis for these interactions remains to be addressed. The aim of this study was to investigate the behavior and circadian gene expression in brain regions previously associated to suicide, after an increasing photoperiod, using a mouse model paradigm. **Methods**: Male C57BL/6 mice were exposed to a gradual transition (+1h/day) from short (Light-Dark 8:16) to long (LD16:8) photoperiod (TSL). Mood disorders were assessed by the open field (OFT), elevated plus maze (EPM), forced swimming (FST) (12:12LD=18 / TSL=17) and tail suspension (TST) (12:12LD=9 / TSL=10) tests, besides the evaluation of spontaneous locomotor activity (SLA) rhythm (TSL=16). Circadian expression of *Per2* and *Bdnf* were evaluated in the striatum and medial prefrontal cortex (mPFC) (n=24 for each group). **Results**: TSL group presented an increased locomotor activity in the OFT periphery (p=0.0128), reduced immobility time in FST (p=0.0083), and a trend towards lower immobility in TST (p=0.0535), compared to the 12:12LD group, suggesting an antidepressant-like behavior. *Per2* and *Bdnf* presented a decreased overall expression in mPFC and non-detectable rhythms in the striatum. These alterations happened without an apparent disruption in SLA. **Conclusion**: The observed phenotypes can be associated with major neurological rearrangements induced by seasonal changes in the light-dark cycle, triggering mania and suicidal behavior in susceptible individuals.

Keywords: Circadian, Seasonal, Suicide, Antidepressant, Photoperiod, Bdnf

INTRODUCTION

Suicide is one of the leading causes of death worldwide (World Health Organization 2014). Interestingly, suicidal behavior is also a seasonal phenomenon as evidenced by an increased prevalence of attempted and completed suicides mainly during spring and summer (Coimbra *et al.*, 2016; Woo, Okusaga, and Postolache 2012). Similarly, mania symptoms in bipolar disorder (BD) presented the same seasonal profile, which could precipitate suicidal acts during this period (Geoffroy *et al.*, 2014). Knowing temporal trends for mania and suicide can lead to new preventive strategies. On this regards, the interaction between seasonal environmental factors and the neurobiology could bring insights for the understanding of its causes and risk factors. However, the biological research on this intriguing observation is still scarce.

A possible explanation for this periodic occurrence relies on the seasonal modulation of the circadian system by the environmental light (LeGates, Fernandez, and Hattar 2014). Circadian rhythms in mammals comprises an integrated multilevel system of oscillators capable of sustain an approximately 24h period of physiology and behavior. At the molecular level, it is driven by activating (mainly BMAL1-CLOCK/NPAS2 heterodimers) and repressing (mainly PERs-CRYs heterodimers) transcriptional/translational feedback loops. At the system level, the peripheral oscillators are subordinated to the suprachiasmatic nucleus (SCN) in hypothalamus, which synchronizes multiple endogenous rhythms to light (Hastings, Maywood, and Brancaccio 2018).

Many processes are under circadian control, including sleep–wake behavior, hormone secretion, cell cycle and gene expression (Bedrosian and Nelson 2017). Correspondingly, several diseases have been related to disruptions of the circadian rhythms, including BD (Bedrosian and Nelson 2017; Wirz-Justice 2018; Oliveira *et al.*, 2018; Nováková *et al.*, 2015). Therefore, circadian rhythm disturbances triggered by environmental light variations in vulnerable individuals could evoke pathological behaviors. In fact, the seasonality observed in certain diseases, such as Seasonal Affective Disorder (SAD), has been directly associated to the photoperiodic condition (Geoffroy *et al.*, 2014; Bedrosian and Nelson 2017; Wirz-Justice 2018). On the other hand, an advance in the circadian phase induced by the morning exposure to bright light has been used for the treatment of depressive patients (LeGates, Fernandez, and Hattar 2014; Lam *et al.*, 2016).

Suicidal behavior was also associated with circadian rhythms. Evening-type subjects are more likely to present higher impulsivity and violent suicide attempts (Selvi *et al.*, 2011), proneness to the onset of major depressive disorder (Selvi *et al.*, 2010) and higher suicide ideation (Bahk, Han, and Lee 2014). Sleep disturbances represent a risk factor for suicidal thoughts and behavior as well (Pigeon, Pinquart, and Conner 2012). The clock gene *PER1* was represented amongst the top predictive biomarkers of suicidality through a convergent functional genomics approach (Levey *et al.*, 2016). Moreover, associations between polymorphisms in clock genes (*CLOCK*, *TIMELESS*, *PER3*) and suicidal behavior were reported in bipolar patients (Oliveira *et al.*, 2018; Pawlak *et al.*, 2017).

The association between seasonality of suicidal behavior and climatic variables have been reported (Akkaya-Kalayci *et al.*, 2017; Vyssoki *et al.*, 2014). Recently, in a large worldwide dataset, increasing solar insolation during springtime was demonstrated to be associated with an early onset of mania episodes in BD (Bauer *et al.*, 2017).

Animal models have been used to explore changes in behavior and physiology in response to different light regimens (LeGates, Fernandez, and Hattar 2014; Otsuka *et al.*, 2014; Goda *et al.*, 2015; Green *et al.*, 2015). Experiments in mice submitted to different photoperiod protocols have shown changes in the expression profile of circadian genes in SCN and other brain regions, mainly in long photoperiods (Evans *et al.*, 2013, 2015). However, the photoperiodic effect on animal models for behaviors related to suicidal behavior in humans has not been explored so far.

In this work, C57BL/6J mice were exposed to a gradually increasing photoperiod protocol resembling the seasonal conditions reported on the aforementioned epidemiological studies. Using this experimental paradigm, we investigated anxiety and depression-like behaviors, spontaneous locomotor activity (SLA) rhythm and circadian gene expression in brain regions previously associated to suicide, as prefrontal cortex and striatum (Pandey *et al.*, 2018; Fitzgerald *et al.*, 2017; Zhang *et al.*, 2014). For molecular analysis, we selected *Period 2 (Per2*), a core component of the molecular clock; and *Brain derived neurotrophic factor* (*Bdnf*), a clock controlled gene with circadian expression in different brain regions (Coria-Lucero *et al.*, 2016). Indeed, *Per2* has been used as a marker for circadian rhythms (Evans *et al.*, 2015); whereas *Bdnf* has been reported downregulated in BD and suicidal patients (Karege *et al.*, 2005; Oquendo *et al.*, 2014; Pandey *et al.*, 2008; Malhi *et al.*, 2018).

MATERIALS AND METHODS

Animals and locomotor activity monitoring

Six weeks old male C57BL/6J mice were obtained from the Central Biotery of Federal University of Alagoas (UFAL), Brazil. The animals were adapted to laboratory conditions of a 12:12h light–dark (LD) cycle for 1 week prior to experiments. Zeitgeber Time (ZT) 0 corresponds to lights-on. Animals were individually placed in opaque cages with wheel-running, transferred to cabinets with individualized ventilation and exhaustion system, and monitored in controlled light (100 lux) and temperature (23±2°C) conditions, with food and water *ad libitum.* Diurnal SLA was analyzed routinely by an infrared sensor system placed 15 cm above the cage lids and automatically recorded in a computer every 5 minutes by the SAP System (Rodrigues, MC, UFRN, Brazil, 2011). All procedures were approved by the Committee on Ethics from UFAL (permit number: CEUA 56/2015).

Photoperiod protocol

After 8 days in 12:12LD, mice were exposed to a short photoperiod (8:16LD) for an additional 8 days for adaptation. Subsequently, animals were submitted to an increasing 1h gradual transition in photoperiod during 8 days (30 minutes both at the beginning and at the end of the light cycle) until a 16:8LD condition (Figure 1). This Transition Short-Long (TSL) protocol was designed to mimic photoperiodic seasonal variations in the environmental light (from winter to summer) associated with suicidal behavior. The control group represents the equinox photoperiod (12:12LD). Temperature was maintained constant throughout the experiment.

Behavioral tests

On the 23rd day of the protocol (penultimate day of the experiment), mice were submitted to the open field test (OFT), and the remaining tests were performed in the following day (Figure 1). The OFT was performed with an apparatus consisting of a square base (40x40cm) divided into 16 compartments (10 x 10cm each) and surrounded by gray plastic opaque walls 40cm high. Mice (12:12LD=18, TSL=17) were allowed to explore the apparatus for 5 min.

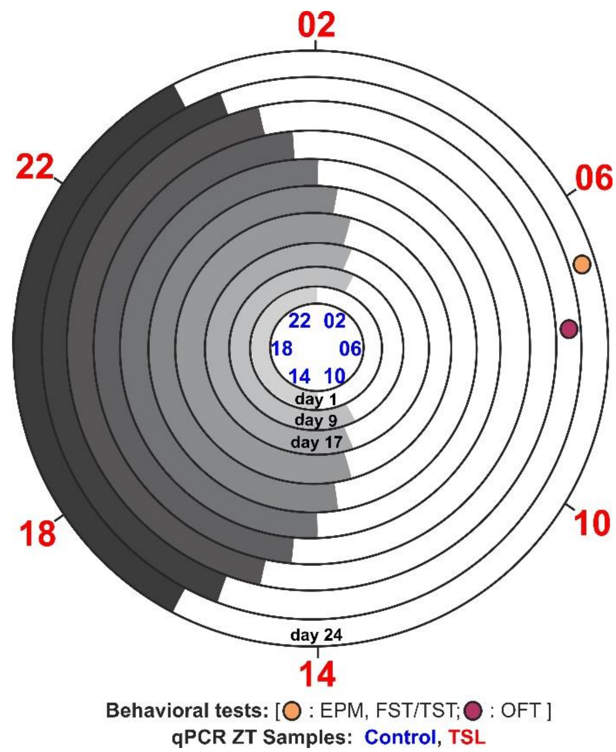

Figure 1. Photoperiod protocol used for behavioral and molecular tests. Each concentric circle represents a photoperiodic condition. After 8 days in 12:12LD, Transition Short-Long (TSL) group was submitted to a short photoperiod (8:16LD) for 8 days, followed by a gradual transition (+1h/day) to a long photoperiod (16:8LD). Tissue sampling for molecular tests was carried out at 6 time points for each group (both TSL and 12:12LD at the 24th day). Behavioral tests were performed between ZT6-8. OFT was performed at the 23rd day and EPM, FST and TST at the 24th day. OFT: open field test, EPM: elevated plus maze, FST: forced swimming test, TST: tail suspension test. Dark phase in gray.

The elevated plus maze (EPM) consisted of two open arms (30x10cm) crossed at right angles with two opposed arms of the same size enclosed by wooden walls 30cm high. The central area (5x5cm), where the arms crossed, was not enclosed. The whole apparatus was elevated 50cm above the floor. To prevent mice from falling, a rim of wood (0.5cm high) surrounded the perimeter of the open arms. Mice (12:12LD=18, TSL=17) were allowed to move freely within the apparatus for 5 min.

In the forced swim test (FST), the mice (12:12LD=18, TSL=17) were placed in a transparent cylindrical glass filled with water at 24°C, 25cm depth for a 7min session. Behavior was recorded and the floating (immobility) time was counted during the last 5min of the test.

We used an additional batch of 19 (12:12LD=9, TSL=10) animals for Tail Suspension Test (TST), in which mice were suspended by the tip of the tail in a rod with adhesive, 30cm above the base, for 7min. The immobility time was measured during the last 5 min, with the first two minutes for habituation. All tests were performed between ZT6-8 (during light phase for both groups).

Tissue preparation and qRT-PCR

A different batch of animals submitted to the same photoperiod protocol was used for molecular assays. Mice were euthanized by cervical dislocation and decapitated to extract medial prefrontal cortex (mPFC) and striatum samples (Li 2011). Tissue sampling was carried out at ZTs 02, 06, 10, 14, 18 e 22 (n=24, 4 per time point) for each group. Sampling was performed at the last day of the protocol, corresponding to 16:8LD for TSL or 12:12LD for control.

Tissue samples were weighed, dissolved in 750 µL of TRIzol LS Reagent (Thermo Fisher Scientific, USA) using a 5 mL syringe and processed as previously reported (Figueredo *et al.*, 2017). Basically, all samples were normalized to the lowest concentration obtained across the two groups for each structure and extraction procedure was carried out controlling pipetting volumes thereafter (Figueredo *et al.*, 2017).

cDNA synthesis were performed with First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, USA), according to manufacturer's protocol, in a final volume of 30 µL using the same RNA volume for each sample. All cDNA samples were diluted (1:10) in RNase free water. qPCR reactions were performed using StepOne Plus (Applied Biosystems, Foster City, CA, USA) using the same parameters described above (Figueredo *et al.*, 2017). All reactions were performed in duplicates considering only cycle thresholds (CT) with standard deviation (SD) <0.5. For efficiency tests of primer pairs, the pooled cDNA was diluted 5x (1:2; 1:4; 1:8; 1:16 and 1:32). The efficiency value was determined by the StepOne Software (Applied Biosystems, Foster City, CA, USA). Only primers with PCR efficiency between 90-110% and with a single melting curve were considered for experiments. The primers were designed in Oligo Explorer (*Per2*) (Fw – 5' CATATCTTCTACCGTCTCTAGCTCG 3' and Rv – 5' GCTACAGCAGCACCATCGTG 3') or obtained from Primer Bank (*Bdnf*) (https://pga.mgh.harvard.edu/primerbank/) (Fw – 5' TCATACTTCGGTTGCATGAAGG 3' and Rv – 5' AGACCTCTCGAACCTGCCC 3'). Sequence alignments were performed using blast (http://blast.ncbi.nlm.nih.gov/Blast.cgi) to verify the specificity.

Data analysis

The SLA was evaluated through the software El Temps v1.294 (http://www.el-temps.com) for the analysis of the onset of motor activity and alpha (activity duration). The total daily activity, L5 (5h of lower activity), M10 (the 10h most active) and RA (Relative Amplitude = (M10-L5)/(M10+L5)) were calculated (Dowling *et al.*, 2005; Witting *et al.*, 1990). Amplitude and acrophase were obtained using Cosinor v1.0 (http://www.circadian.org). The coefficient of variation (CV) was used to measure the onset activity dispersion.

The SLA parameters for the TSL group were evaluated on specific days selected to represent each photoperiodic regime: mean data from the 5th and 6th day for 12:12LD, day 16 for 8:16LD and day 23 (last day with full record from TSL) for 15:9LD. In each animal, the data from each hour were normalized by the average data of the corresponding day (normalized data by animal = [data every hour in day x] / [average of the data in day x]). Datalog from single animals presenting variations across the days due to sensor registry were excluded from this analysis. Radial plot with mean data for each of these conditions was used to generate visual representation of the transitions in SLA, using plotrix package for R. Paired data were analyzed as repeated measures One-Way ANOVA with Dunnett´s multiple comparisons test. Difference between means in the behavioral groups was analyzed through the t-test, with 95% of confidence interval and a significance level of $p<0.05$.

Gene expression analysis was performed using the CT (Cycle Threshold) data converted into $(2^{-CT})_x(10^{10})$, as previously described (Figueredo *et al.*, 2017). Multiple t-test was used to compare time points between groups. The graphics and calculations were performed using the GraphPad Prism v6.0 and IBM *SPSS* v*20*, CircWave v1.4 (http://www.euclock.org/results/item/circ-wave.html) and Cosinor softwares. To investigate oscillatory patterns in gene expression and to calculate rhythmic parameters (acrophase, amplitude and mesor), we used the cosinor regression test adjusted for a fixed 24 hours period (Refinetti, Lissen, and Halberg 2007). The peak-to-trough ratio (P/T) was calculated by: [peak]/[trough]. Peak = Mean of ZT with highest expression; and Trough = Mean of ZT with lower expression. Differences in the P/T were evaluated by t-test.

RESULTS

Increased photoperiod disrupts *Per2* and *Bdnf* expressions in mPFC and striatum, without disturbing locomotor activity rhythm

We initially evaluated the SLA profile, the gold standard marker for rhythmic outputs, from mice during the TSL protocol (Figure 2A). A large dispersion on the activity onset was observed in the abrupt change from 12:12LD to 8:16LD, as a result of the transient period of adaptation to the new regime (days 9 to 13, Figure 2B). On the 16th day, the data dispersion returns to the same level of the equinox photoperiod. In the 8:16LD to 16:8LD transition, mice presented a decreased dispersion level concerning the onset of SLA in response to light synchronization. These data indicate that animals are properly synchronizing their SLA each day in the TSL condition. Correspondingly, there was a phase shift in the SLA onset between groups (day 6 =18.2±0.2; day 16 =16.2±0.1; day 23 =19.8±0.4; $p<0.0001$) (Figure 2B, C) and no detectable differences in the phase angle of entrainment (Figure 2D).

The acrophase from the short photoperiod was significantly shifted in 2h (day 6 =22.7±1.3; day 16 =20.8±1.0; $p<0.001$) (Figure 2D). After the TSL, the activity was delayed by 2.5h compared to the short photoperiod condition (day 23 =23.3±1.1; $p<0.001$) (Figure 2C, D). The activity duration (alpha) was diminished in the long photoperiod (day 23= 493±48; day 16 =673±130; day 6 =694±104; $p<0,0001$), though without changing the total activity or amplitude (Figure 2D). The L5, M10 and RA indices did not show significant differences either.

Further, we confirmed a daily expression pattern for *Per2* and *Bdnf* in mPFC and striatum of mice under a 12:12LD regime (Figure 3A-D). However, after the TSL protocol, their rhythmic profile were disrupted (Figure 3B-D), except for *Per2* in mPFC (Figure 3A). Despite this, *Per2* amplitude was dramatically decreased (91.3 fold) and there was a 2h phase shift in the fitted curve acrophase in mPFC (Table 1). There were also corresponding shifts in the peak ZT for each gene in the TSL group (Table 1).

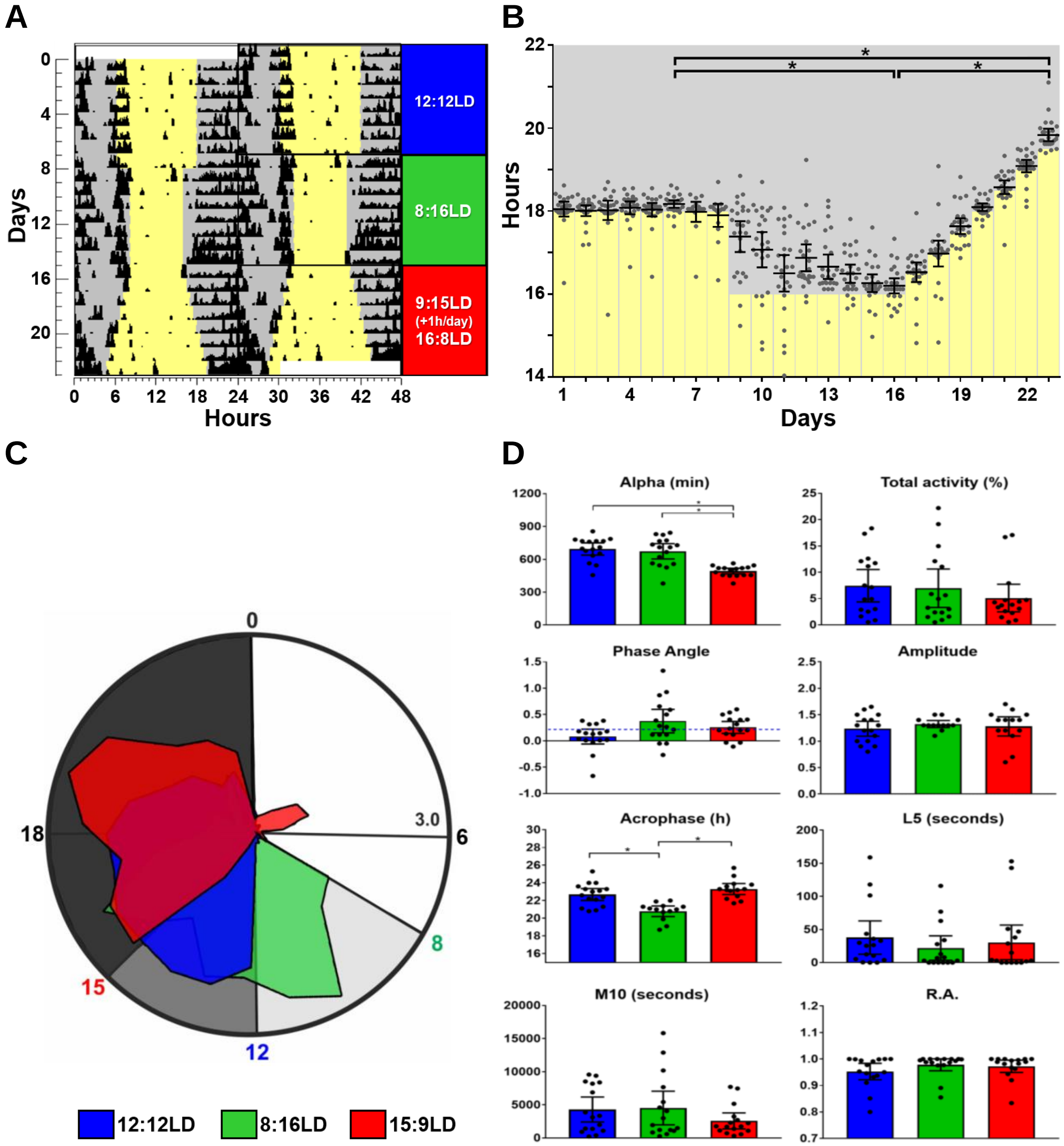

Figure 2. Locomotor activity profile of 23 days from mice during a short-to-long transition photoperiod (TSL group). **A** - Representative actogram showing the different stages of the protocol (8 days in 12:12LD; 8 days in 8:16LD; 7 days in TSL). The last (24th) day in TSL protocol was not registered for SLA due to behavioral tests. Activity is represented as black bars; yellow indicates light phase and gray, dark phase). **B** - Positive flanks, representing the SLA onset, evaluated across 23 days. Mean with 95% of confidence interval. **C** - Radial plot indicating the normalized mean activity profile from animals exposed to different photoperiodic conditions. Numbers indicate ZTs. ZT0 represents lights on for each condition. Grey area represents the dark phases, starting at different ZTs depending on the stage of the TSL protocol. **D** - Locomotor activity parameters for representative days for each photoperiodic conditions: Activity duration (alpha),

total activity, phase angle of entrainment, amplitude and acrophase from fitted cosine curves, L5 (5h of lower activity), M10 (the 10 most active hours) and RA (Relative Amplitude). Data as mean with 95% CI. Repeated measures One-Way ANOVA with Dunnett´s multiple comparisons test.

Considering individuals ZTs, a significant downregulation in *Per2* (Figure 3A) ($p<0.001$) at ZT14 and ZT18, and Bdnf (Figure 3C) at ZT6, ZT14 and ZT18 were observed in mPFC for TSL. Also, the circadian rhythm was not detected for *Bdnf* in the mPFC (Figure 3C) and for both genes (Figure 3B, D) in the striatum for the TSL group. Moreover, a significant downregulation of the overall expression level was observed in mPFC (Figure 3E) but not striatum (Figure 3F) in the TSL for both genes.

Mice exposed to a gradually increased photoperiod present an antidepressant-like behavior

We assessed anxiety and depression behaviors in animals exposed to TSL and 12:12LD conditions (Table 2). While the parameters attributed to depression and anxiety did not present any change, a slight increased ambulation on the periphery was observed in OFT, accounted for the number of crossed squares (12:12LD=82.7±21.9; TSL=107.5±36.3; $p=0.0128$) and the locomotion speed (12:12LD=31.3±9.0; TSL=39.3±13.0; $p=0.0380$), which may suggest an antidepressant-like effect (Table 2, Figure 4A, B).

The experimental group also exhibited a lower immobility time in the FST (12:12LD= 135.5±67.6; TSL= 78.9±35.0; $p=0.0042$; Figure 4C) and a trend towards lower immobility (12:12LD= 209.8±24.9; TSL= 167.5±46.2; $p=0.0535$; Figure 4D) in the TST, which have also been associated with an antidepressant-like effect in rodents. For TST, we used a different batch with fewer animals, which may have impaired the detection of statistical significance in this essay. No other significant changes in behavior were observed.

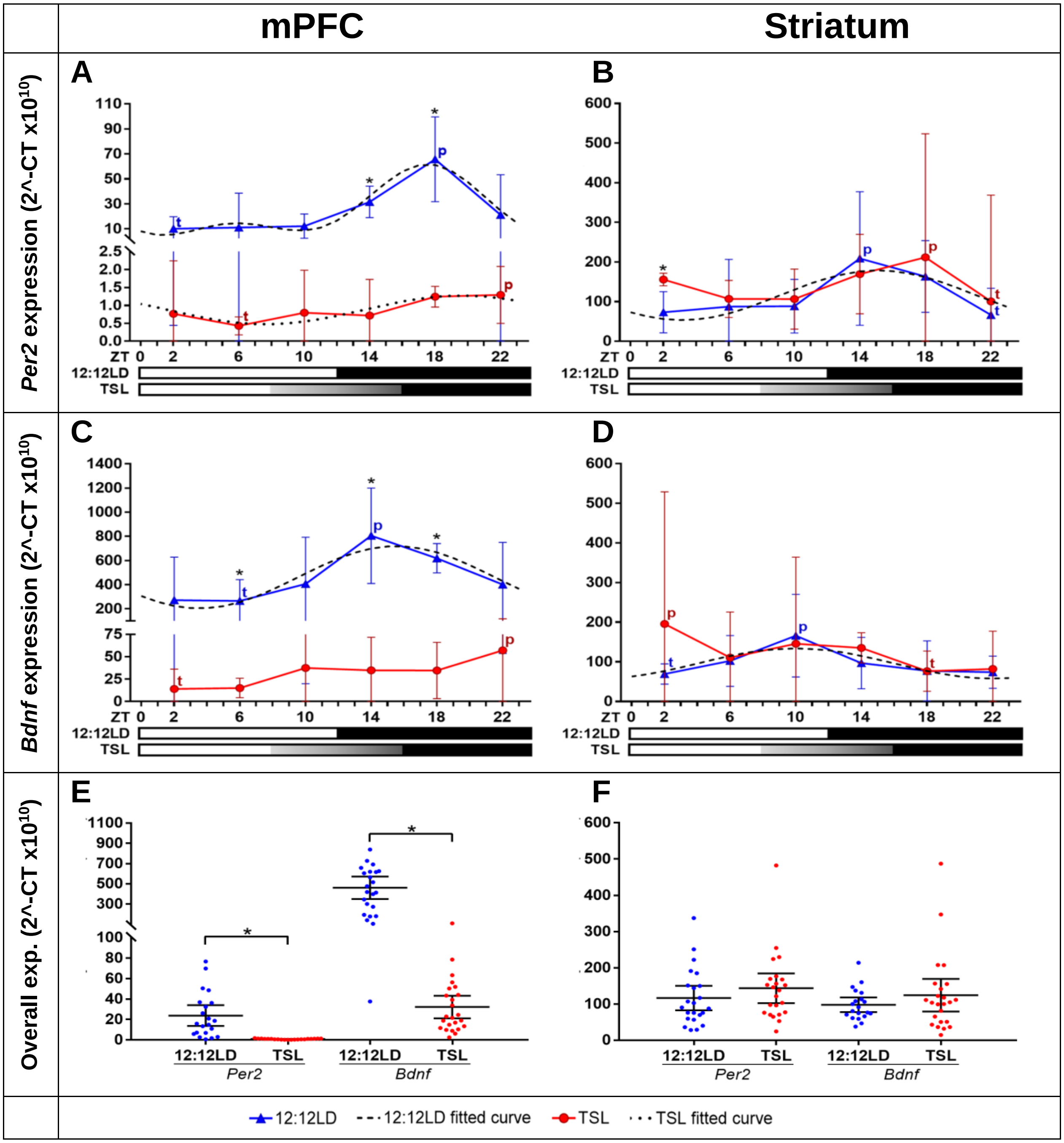

Figure 3. *Per2* and *Bdnf* expression in mPFC and striatum from 12:12LD and TSL (n=24 for each group). Diurnal expression profile of *Per2* (**A**, **B**), *Bdnf* (**C**, **D**), and overall expression (**E**, **F**). Each dot in **E** and **F** represents a single sample isolated in different Zeitgeber Times (ZTs). Data are shown as mean with 95% CI. 2^{-CT} (CT= Cycle Threshold) data were adjusted to cosine function and represented as dashed curves. The asterisk indicates difference between 12:12LD and TSL ($p<0.05$) in each ZT after multiple t test analysis. Horizontal bars indicates ZT for each protocol (white: light phase; black: dark phase; gray: dark phase from transition period). Samples were normalized independently for each structure, as previously described (Figueredo *et al.*, 2017).

Table 1. *Per2* and *Bdnf* rhythmic expression parameters in mPFC and striatum for each condition.

Rhythmic Parameter	mPFC				Striatum			
	Per2		***Bdnf***		***Per2***		***Bdnf***	
	1212LD	TSL	1212LD	TSL	1212LD	TSL	1212LD	TSL
Acrophase	17.5	19.6	15.5	-	15.1	-	10	-
Amplitude	36.5	0.4	257.8	-	62.7	-	37.9	-
Mesor	25.2	0.9	461.4	-	116.1	-	9.6	-
P/T	6.5*	3.0*	3.0*	4.1	3.1	2.1	2.4	2.5
Peak ZT	18	22	14	22	14	18	10	2

P/T: peak-to-trough ratio. 1212LD: control group. TSL: Transition Short to Long group.
Peak ZT: Zeitgeber Time with the highest expression value. *$p<0.05$.

Table 2. Behavioral variables assessed for anxiety and depression in the Open Field Test (OFT), Elevated Plus Maze (EPM), Forced Swim Test (FST) and Tail Suspension Test (TST).

Behavioral Parameters	12:12LD Mean (SD)	TSL Mean (SD)
OFT	**(n=18)**	**(n=17)**
Time spent in periphery (sec)	266.6 (19.8)	273.2 (10.8)
Number of squares crossed in periphery	82.7 (21.9)	107.5 (36.3)*
Time spent in center (sec)	33.4 (19.8)	26.9 (10.8)
Number of squares crossed in center	8.4 (4.8)	8.2 (3.6)
Number of crossing between center and periphery	25.9 (13.8)	24.1 (10.4)
Total number of squares crossed	116.9 (35.4)	139.8 (45.2)
Center latency (sec)	43.8 (55.8)	44.5 (35.6)
Immobility time (sec)	23.9 (22.9)	12.8 (8.1)
Immobility frequency	8.2 (4.0)	6.8 (2.9)
Speed on periphery (squares/sec)	31.3 (9.0)	39.3 (13.0)*
Speed on center (squares/sec)	25.6 (6.6)	31.5 (11.0)
General speed (squares/sec)	39.0 (11.8)	46.6 (15.1)
Time spent rearing (sec)	40.3 (13.4)	47.3 (12.5)
Number of rearing	36.3 (11.3)	37.2 (11.1)
Time of stretched attend postures (sec)	1.0 (1.7)	1.1 (1.1)
Number of stretched attend postures	1.6 (2.2)	1.8 (1.5)
Number of defecation pellets	0.7 (1.2)	0.9 (1.7)
Time spent grooming (sec)	5.5 (3.0)	7.7 (7.5)
Number of grooming	1.9 (1.0)	2.8 (2.9)
EPM	**(n=18)**	**(n=17)**
Time spent in open arms (%)	6.3 (5.5)	4.5 (4.3)
Number of open arm entries (%)	11.0 (5.4)	9.1 (5.7)
Time spent in center (%)	19.1 (8.8)	18.2 (4.9)
Number of center entries (%)	48.9 (2.7)	49.5 (0.9)
Time spent in enclosed arms (%)	74.6 (11.7)	77.3 (7.7)
Enclosed arms entries (%)	40.1 (5.4)	41.4 (5.4)
Time spent rearing (sec)	12.2 (4.7)	13.6 (5.5)
Number of rearing	13.1 (4.7)	15.4 (6.2)
Stretched attend postures time (sec)	21.0 (7.9)	18.6 (6.4)
Number of stretched attend postures	13.7 (5.8)	12.9 (2.8)
Head dipping time (sec)	7.5 (4.4)	6.5 (3.5)
Number of head dipping	8.2 (3.9)	7.0 (3.4)
Grooming time (sec)	2.5 (2.5)	4.5 (3.7)
Number of grooming	0.9 (0.9)	1.1 (0.9)
FST	**(n=18)**	**(n=17)**
Immobility time (sec)	135.5 (67.6)	78.9 (35.0)*
TST	**(n=9)**	**(n=10)**
Immobility time (sec)	209.8 (24.9)	167.5 (46.2)#

The asterisk indicates statistical difference between 12:12LD and TSL groups.

*p<0.05; #p=0.0535. Mean with SD. Mann-Whitney test.

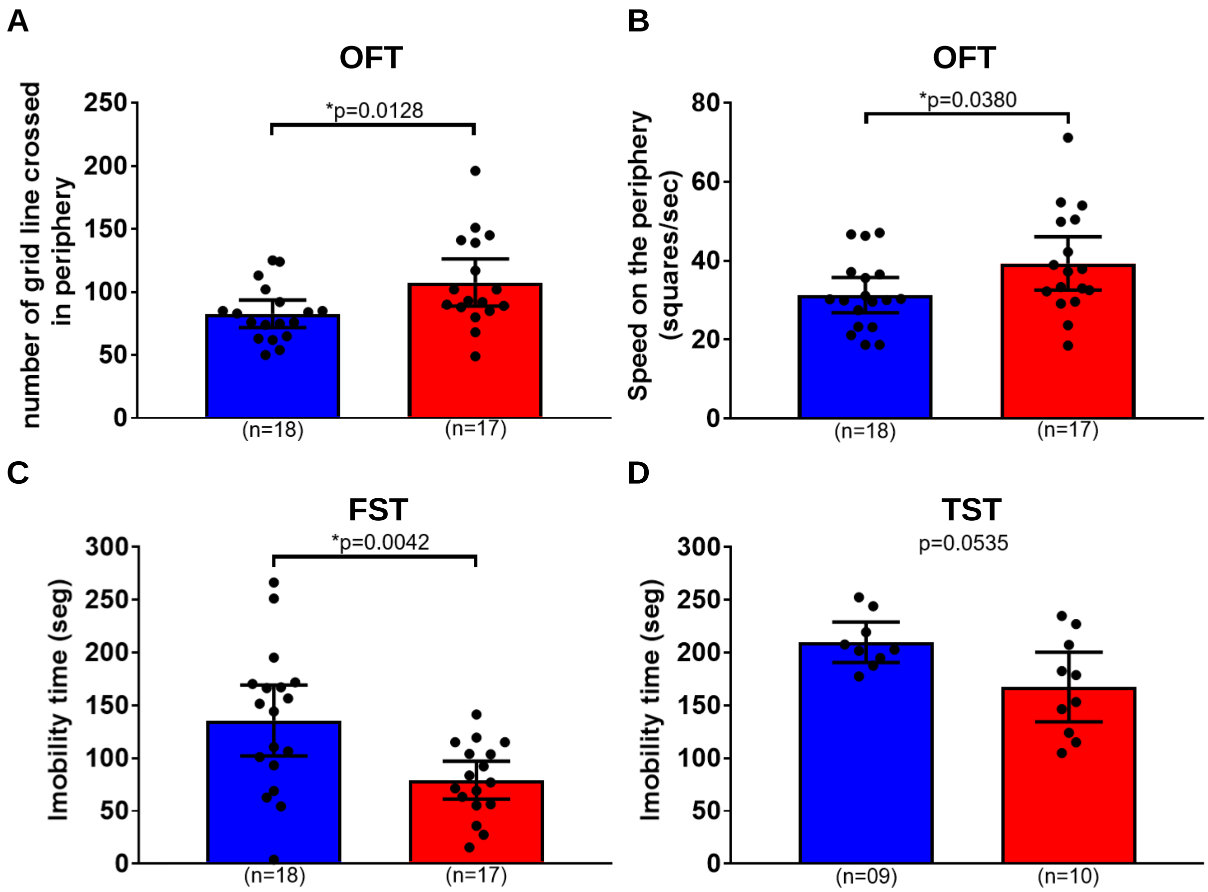

Figure 4. Behavioral parameters indicating an antidepressant-like effect in TSL group. Increased ambulation (**A**) and speed (**B**) in the Open Field Test - OFT periphery; a lower immobility in the forced swimming test – FST (**C**), and a trend for lower immobility in the tail suspension test - TST (**D**). Mean with 95% CI, Mann-Whitney test. Blue, 12:12LD; Red, TSL.

DISCUSSION

Suicide is a major global health problem and, curiously, emerges worldwide in populations as seasonal changes, mostly associated with environmental light. Despite the known association between winter and depression (Bedrosian and Nelson 2017), and depression and suicide (Woo, Okusaga, and Postolache 2012; Selvi *et al.*, 2010; Pawlak *et al.*, 2017), there is, against the common sense, a higher occurrence of suicidal behavior at late spring/early summer (Coimbra *et al.*, 2016; Woo, Okusaga, and Postolache 2012).

Therefore, longer photoperiods could trigger an improvement in mood (Wirz-Justice 2018), but also a concomitant suicidal act (Vyssoki *et al.*, 2014). This hypothesis is strengthened by observing the seasonality of hospitalizations for manic episodes, which increases during spring/summer (Parker, Hadzi-Pavlovic, and Graham 2017). In a recent multi-center study encompassing 32 countries of various latitudes, a strong inverse association between monthly increase in solar insolation in springtime and the age of onset of BD type I was identified (Bauer *et al.*, 2017). However, although the short photoperiod effect on mood as a susceptibility factor for depression has been explored (Otsuka *et al.*, 2014; Green *et al.*, 2015), the biological basis for the seasonal association of longer day lengths with antidepressant-like effect and suicidal behavior is still neglected. Moreover, the majority of the protocols using animal models did not consider the transitional effect of the natural environment, which may contribute for this shortfall.

Herein, we implemented a switching photoperiod protocol (short to long) in order to mimic the environmental conditions previously reported to be associated with suicide. We initially observed that the synchronization of SLA to light was not disturbed and, consistently, there was a corresponding shift in the acrophase compared to the previous short photoperiod exposure. Moreover, the amplitude of SLA was maintained despite of a shorter alpha. Since SLA reflects the sum of the peripheral and central oscillators outputs, this suggest that the protocol did not provoke an uncoupling event between the structures responsible for this output. However, we observed that the temporal expression of *Per2* was abolished in striatum and significantly downregulated in mPFC. These results are similar to what was observed in *Per2:Luc* mice exposed to a long photoperiod (20:4LD), with decreased amplitude of *Per2* in different brain areas (Evans *et al.*, 2015). Similarly, a disrupted environmental LD cycles abolishes the circadian expression of peripheral clock genes in liver, without inducing behavioral arrhythmicity in mice (Oishi *et al.*, 2015).

On the other hand, the *Per2* expression changes in the mPFC and striatum could be related to altered outputs from these structures, including mood disorders (Drevets, Price, and Furey 2008). In fact, after exposure to an increasing photoperiodic condition, animals demonstrated an antidepressant-like behavior, characterized by the reduction in immobility time during the FST and increased locomotion in exploratory tests. To the best of our knowledge, the photoperiodic induction of an antidepressant-like effect in C57BL/6 mice had not been reported yet. Molina-Hernandez (2000) described a reduced immobility time in FST of male wistar rats exposed to a long photoperiod (14:10LD) with similar effect of the antidepressant drug group (clomipramine and desipramine), when compared to the equinox group (12:12LD) (Molina-hernandez and Tellez-alcantara 2000).

As long photoperiod exposure develops antidepressant-like behavior in animals, the spring/summer period may be contributing to an antidepressant and/or manic effect in humans. Interestingly, several studies show the association between the use of antidepressant drugs and the risk of suicide in depressed youth (Larsson 2017; Plöderl and Hengartner 2018; Coupland *et al.*, 2015). Therefore, these evidences point to the beneficial antidepressant effect of light, but in susceptible individuals, may increase the risk of suicide attempts.

In mice, the disruption of core clock components alters the circadian rhythm and consistently elicits aberrant behaviors resembling those of human affective disorders (Landgraf *et al.*, 2017). The *ClockΔ19* mutant mice present a behavioral phenotype characterized by hyperactivity, decreased anxiety and depression-like behavior, and increased preference for rewarding stimuli, which is highly consistent with mania in humans (Kristensen, Nierenberg, and Østergaard 2018). On the other hand, the Myshkin mouse model of mania, with a heterozygous inactivating mutation in the neuron-specific Na^+/K^+-ATPase (NKA) α3 subunit, demonstrates profound circadian and light-responsive behavioral alterations independent of molecular clock disruption, highlighting the importance of synchronization pathways for mood and behavior (Timothy *et al.*, 2017).

Moreover, a circadian disruption induced by chronically exposing mice to a 10:10LD, causes loss of dendritic length and decreased complexity of neurons in mPFC, accompanied by behavioral changes that suggest cognitive rigidity and impulsivity (Karatsoreos *et al.*, 2011).

Impulsivity and aggression behaviors are risk factors for suicide and are highly related to mania (Gould *et al.*, 2017).

To gain insight about the molecular mechanism underlying this antidepressant-like effect observed in TSL paradigm, we also analyzed the temporal expression of *Bdnf* in mPFC and striatum. *Bdnf* is a member of the neurotrophin family involved in neuronal growth, neuroplasticity and synthesis of proteins for neuronal function and synaptic modulation (Paska, Zupanc, and Pregelj 2013). This gene presents a circadian expression in different brain areas and shows a relevant role in the pathophysiology of many psychiatric disorders, including BD (Autry and Monteggia 2012). We demonstrated that *Bdnf* were significantly downregulated in mPFC and its rhythmic expression was disrupted in both structures. The interference in *Bdnf* expression, as observed herein, may have a significant impact on brain function (Karpova 2014). In fact, studies in post-mortem brain of teenage and middle age suicide victims showed a decrease in BDNF levels in prefrontal cortex and hippocampus compared with normal control subjects (Karege *et al.*, 2005; Pandey *et al.*, 2008).

Although animal models have been explored and provided insights for the mechanism and treatment for psychiatry disorders, there are several limitations in this approach considering the translational perspective. Being essentially a human behavior, the reproduction of motivation, conscious planning and the suicidal act are activities practically impossible to obtain from animal experiments. Therefore, experimental models simulate only some aspects of suicidal endophenotypes (Gould *et al.*, 2017). Moreover, mice are nocturnal animals in laboratory settings, which contrasts with human diurnality and possibly with the downstream photic synchronization mechanisms (LeGates, Fernandez, and Hattar 2014; Goda *et al.*, 2015). Although the current protocol takes advantages of the transitional effect simulating seasonality, it cannot be directly compared to the literature since the majority of the published studies used stable photoperiods over days or weeks, with different light regimes (Goda *et al.*, 2015; Green *et al.*, 2015; Evans *et al.*, 2013). Furthermore, a higher temporal resolution would be more sensitive to detect changes in phase, period and amplitude of gene expression.

Despite these limitations, this is the first report to demonstrate disturbed circadian expressions of *Per2* and *Bdnf* in mouse mPFC and striatum after exposure to a condition mimicking the seasonal environmental changes associated with suicidal behavior. These modifications could predispose the brain for an impaired functioning, affecting cognition and behavior. Accordingly, these animals showed an antidepressant-like effect induced by the increased photoperiod, which may open new opportunities for the development of animal models for BD and suicide. The mechanism by which these entraining conditions affect the endogenous rhythms in different brain regions and its consequences in behavior still need to be investigated.

The results presented herein and the literature on human brain and behavior (Bedrosian and Nelson 2017; Vyssoki *et al.*, 2014) indicates that the seasonal variation in suicidal behavior can be the tip of the iceberg of a broader interference of light regime in humans. Phototherapy and circadian realignment has been used for the treatment of depression and investigated in suicide (Dallaspezia, Suzuki, and Benedetti 2015), and dark therapy has been recently explored in BD (Phelps 2017). Therefore, the elucidation of the role of natural and artificial variations in light on the modulation of circadian rhythms and behavior can contribute to the pursuit for effective treatments of BD and for suicide prevention.

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CONSIDERAÇÕES FINAIS

A sazonalidade do comportamento suicida é um fenômeno observado em muitos países, independentemente do hemisfério, com pico no final da primavera/início do verão, tanto para suicídios quanto tentativas de suicídio. A ausência de evidências de sazonalidade em regiões / países próximos à linha do Equador reforça o papel da latitude neste comportamento sazonal suicida, assim como observado no Brasil. Dentre os possíveis moduladores desta ritmicidade, o tempo de exposição à luz (duração do dia) tem apresentado destaque, inclusive em experimentos com modelo animal, resultando em alterações moleculares e comportamentais importantes, possivelmente relacionadas ao comportamento suicida. Estes dados mostram a necessidade em conhecer melhor a relação entre os moduladores dos ritmos circadianos, fatores ambientais sazonais e o comportamento suicida para uma intervenção efetiva na incidência sazonal dos casos de suicídio.

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