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Has the Sun Set for Seasonal Affective Disorder and HPA axis Studies? A Systematic Review and Future Prospects.

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ABSTRACT:

Objective: Seasonal Affective Disorder (SAD) is a form of cyclic mood disorder that tends to manifest as winter depression. SAD has anecdotally been described as a hypocortisolemic condition. However, there are no systematic reviews on SAD and Hypothalamic-Pituitary-Adrenal (HPA) axis function. This review intends to summarize these findings.

Methods: Using the PRISMA (2009) guideline recommendations we searched for relevant articles indexed in databases including MEDLINE, EMBASE, PsycINFO, and PsychArticles. The following keywords were used: "Seasonal affective disorder", OR "Winter Depression", OR "Seasonal depression" associated with: “HPA Axis” OR “cortisol” OR “CRH” OR “ACTH”.

Results: Thirteen papers were included for qualitative analysis. Studies used both heterogeneous methods and populations. The best evidence comes from a recent study showing that SAD patients tend to demonstrate an attenuated Cortisol Awakening Response (CAR) in winter, but not in summer, compared to controls. Dexamethasone Suppression Test (DST) studies suggest SAD patients have normal suppression of the HPA axis.

Conclusion: There is still insufficient evidence to classify SAD as a hypocortisolemic condition when compared to controls. Heterogeneous methods and samples did not allow replication of results. We discuss the limitations of these studies and provide new methods and targets to probe HPA axis function in this population. SAD can provide a unique window of opportunity to study HPA axis in affective disorders, since it is highly predictable and can be followed before, during and after episodes subsides.

Keywords: Seasonal Affective Disorder, Winter Depression, HPA axis, cortisol, depression, mood disorder.

1- Introduction

Seasonal affective disorder (SAD) was first described in 1984 as a form of recurrent depression that usually occurs during winter and spontaneously resolves in spring/summer (Pjrek et al., 2016). SAD is usually characterized by atypical features, such as fatigue, hyperphagia, craving for carbohydrate-rich foods and weight gain, putatively energy-conserving symptoms that frequently precede the functional impairments seen afterwards (Gudenas and Brooks, 2013). Another described feature of SAD seems to be an improvement in mood after light therapy (LT) (Nussbaumer et al., 2015a; Perera et al., 2016). Because of controversies regarding the classification of SAD as a distinct condition (Rosenthal, 2009), seasonality is a specifier for both Major Depressive Disorder (MDD) and the depression and hypo/manic episodes seen in Bipolar Disorder (BD) (Severus and Bauer, 2013). Regardless of its classification, the predictability of SAD makes it an ideal condition to prospectively study possible hormonal changes in the context of depression.

The prevalence of SAD in the general population varies between 1-9%; it is especially influenced by latitude(Mersch et al., 1999; Nussbaumer et al., 2015b) and gender, with almost 80% of patients being female (Kasof, 2009). Light exposure has been implicated as a major factor in the pathophysiology of the condition. From melanopsin alterations or genetic variants (Coogan et al., 2015; Roecklein et al., 2009) to increased incidence of SAD in visually impaired people (Madsen et al., 2017, 2016), there is evidence supporting a role for light deprivation in the development of depressive symptoms in these individuals. Light is the main environmental cue for circadian rhythms and stress response, mainly by activation of the suprachiasmatic nucleus (SCN) of the hypothalamus (the human central master clock) and the autonomic and endocrine response that follows (**Fig 1).** The main hormonal component of the stress response involves activation of the hypothalamic-pituitary-adrenal (HPA) axis and consequent glucocorticoid (GC) release (in humans, cortisol). Cortisol is an important epigenetic agent that regulates the expression of a large array of genes (Reul et al., 2015) (**Fig 2**). GC are thought to

regulate approximately 20% of the expressed human genome, and their effects spare no organ or tissue (Chrousos and Kino, 2005).

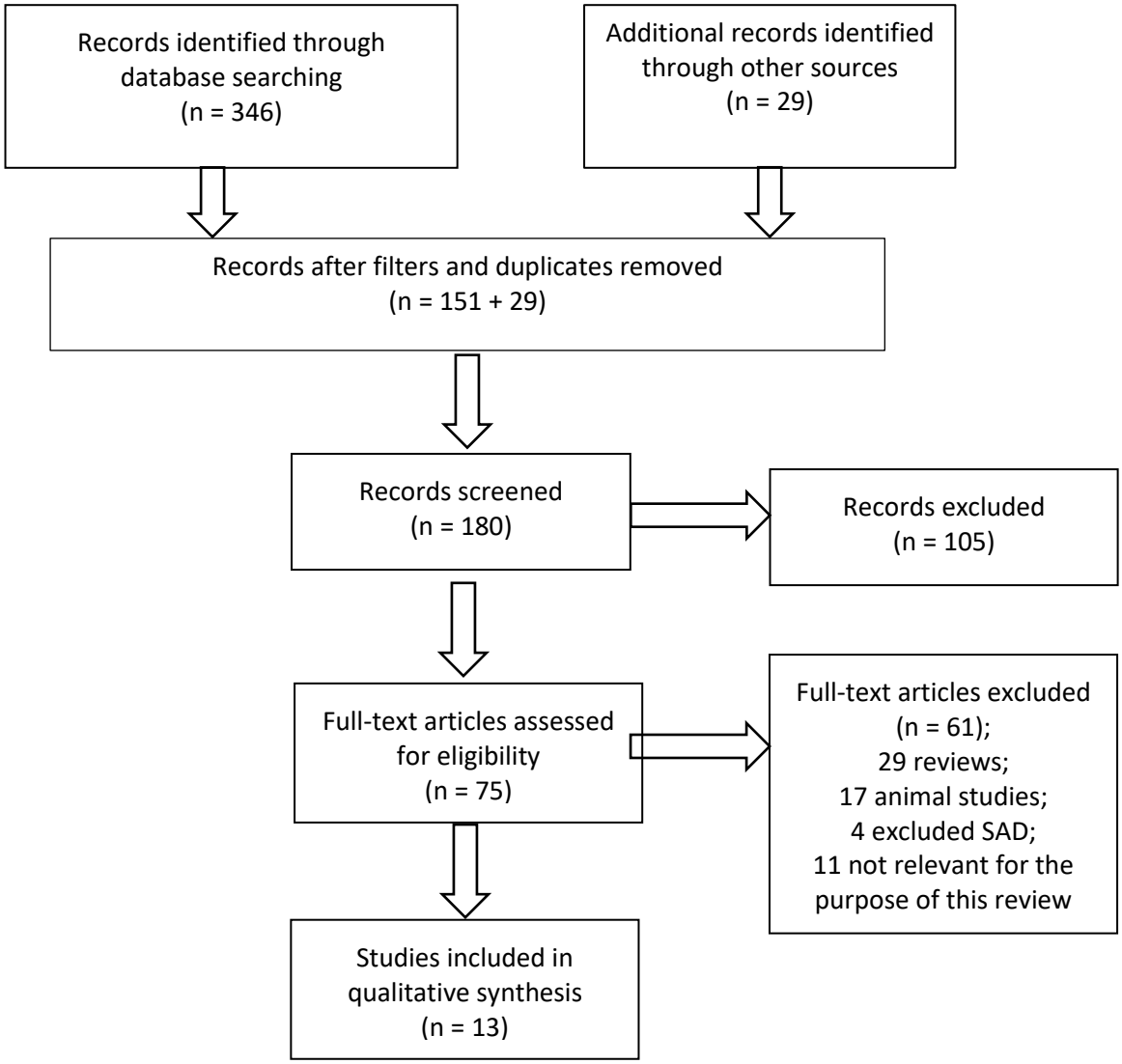
Interestingly, evidence suggests that genetic expression exhibits a circannual pattern, with inverted immune-metabolic profiles observed between the northern and southern hemispheres (Dopico et al., 2015). Participants investigated during winter tend to exhibit a profound pro-inflammatory transcriptomic profile, with elevated levels of C reactive protein (CRP) and increased IL-6 soluble receptors, inflammatory factors previously associated with MDD (Dantzer et al., 2008), BD (Fernandes et al., 2016) and SAD (Leu et al., 2001). Another recent paper shows that neocortical genetic expression is also subject to circadian and circannual (seasonal) effects (Lim et al., 2017). Because of its wide epigenetic and metabolic properties, it is reasonable to believe that cortisol might play a role in these seasonal changes.

However, evidence suggests different HPA axis profiles in distinct depressive subtypes (Gold, 2014; Gold and Chrousos, 2002). While melancholic depression has been consistently associated with hypercortisolism, the same does not apply for depression with atypical features (Mario F Juruena et al., 2017; Lamers et al., 2013). Due to the very similar symptoms of SAD and atypical depression, it has been suggested that both these conditions, along with Chronic Fatigue Syndrome (CFS) (Papadopoulos and Cleare, 2012), are characterized by hypocortisolism (Juruena and Cleare, 2007). In turn, atypical depression has been linked to increased inflammation, an analogous stress response system (Lamers et al., 2013). However, to our knowledge, there are no systematic reviews on SAD and HPA axis function. This review intends to summarize these findings and shed some light on the pathophysiology of this condition.

2- Methods:

Using the PRISMA (2009) guideline recommendations, we searched for relevant articles indexed in databases including MEDLINE, EMBASE, PsycINFO, and PsychArticles, using the Ovid platform. The following keywords were used: "Seasonal affective disorder", OR "Winter Depression", OR "Seasonal depression" associated with: “HPA Axis” OR “cortisol” OR “CRH” OR “ACTH”. We included full-text articles, in humans, written in English language, with no temporal limits, published until September 2018. Animal studies and review articles were excluded from the main analysis but are discussed when thought relevant.

PRISMA FLOW DIAGRAM:



3- Results:

This search strategy resulted in 13 full articles that evaluated the HPA axis function in SAD. Studies had very heterogeneous designs, populations and drug challenges, and followed an interesting chronology **(Table 1).**

3.1: Dexamethasone Suppression Test (DST) Studies:

At his seminal paper of SAD in 1984, Rosenthal et al. describe winter depression in 29 individuals, with spontaneous remission during summer. After performing a DST in 7 of these individuals, during summer and winter, the authors' found normal suppression of the HPA axis in both seasons (Nussbaumer et al., 2015b). A second DST study (1986) by the same group recruited 20 patients (5 male, 15 female) with at least two episodes of SAD (James et al., 1986). Of those, 2 patients had an abnormal DST, while the rest had normal suppression (James et al., 1986). After this second study, the authors concluded that "normal suppression of the HPA axis appears to be a feature of SAD, since SAD patients have normal suppression of the HPA axis after DST" (James et al., 1986).

3.2: 5- Hydroxytryptophan challenge (5HT agonist)

In 1987, the same group set out to test a different approach. They recruited 10 participants with at least 2 years of seasonal depression and compared them to 10 healthy controls (matched by age, sex and menstrual history) (Jacobsen et al., 1987). This time, researchers compared the effects of placebo and a serotonin agonist [5-Hydroxithryptophan (5HTP)] in HPA axis function. At baseline and after placebo, they found higher levels of prolactin ($F=7.83$, $p < 0.02$) and a trend for higher cortisol levels ($F=3.33$, $p=0,09$) in participants with SAD. After the challenge with 5HTP, there were no significant differences between groups. The authors concluded that prolactin and cortisol levels might be elevated in SAD patients, although their sample was very small (Jacobsen et al., 1987).

3.3: Ovine Corticotropin - Releasing Hormone Challenge (oCRH):

During the winter of 1991, Rosenthal's group recruited another 10 SAD patients (5 men and 5 women) depressed at the moment of assessment (Joseph-Vanderpool et al., 1991). Participants were studied under two conditions: light-treated (2.5hs of LT, twice a day, for 9 days, before the infusion) and untreated. Controls were 13 age- and sex-matched healthy individuals. Basal assessment was performed in 7 out of 10 SAD patients (before and after LT) and in 9 controls. On the study day, all subjects received 100 ug of Ovine CRH (oCRH) and had their ACTH and cortisol levels assessed.

Clinical response was statistically significant after LT in SAD patients (Baseline HDRS: 16.4 ± 1.33 vs LT: 7.5 ± 1.10; $p < 0.01$). They also found that cortisol levels were significantly lower in SAD patients at 10 pm (when cortisol levels are usually at their nadir) compared to controls (mean (SD): 46.6 (± 27.6) nmol/L vs 137.9 (± 71.73) nmol/L; $p= 0.02$). They found no significant differences in diurnal levels of ACTH and cortisol between treated and untreated patients.

After the oCRH challenge, untreated SAD patients had a delayed and reduced response to CRH compared to controls (ACTH: SAD 4.4 ± 0.6 pmol/L vs 8.1 ± 1.2 pmol/L; $p=0.02$); (cortisol: SAD 508 ± 27.5 nmol/L vs 583.8 ± 35.3 nmol/L; $p < 0.01$). After 9 days of LT, basal plasma ACTH and cortisol (and their responses to oCRH) showed a trend towards similarity between light-treated SAD participants and controls ($p=0.1$). SAD patients also had a delayed response to oCRH of approximately 30 minutes, compared to controls ($p=0.05$). That difference tended to decrease in the treated group. The ratios of ACTH and cortisol were similar between treated and non-treated groups. The authors hypothesized a possible dysfunctional CRH system in SAD, with blunted adrenal response (Joseph-Vanderpool et al., 1991).

3.4: *d- Fenfluramine Challenge (5HT agonist)*

In 1993, Coiro et al. from the University of Parma, Italy, recruited 7 SAD patients (5 men, 2 women, aged 30-44 years) and compared them with 8 healthy controls (matched by Body Mass Index [BMI]), during summer and winter. SAD patients had a mean score in the HDRS of 19.2 during winter and 2.5 during summer. The study aimed to investigate the hormonal effects of 60 mg of d-Fenfluramine (5HTa), compared to placebo. At baseline, there was no difference between hormone levels in both groups. After the challenge with d-Fenfluramine, SAD patients displayed a blunted HPA axis response to the drug, with lower cortisol levels than controls, regardless of the season (Summer/Spring $F=7,39$; $p < 0.05$;

Fall/Winter F=7,5; $p < 0.02$). There were no differences between groups when using placebo as challenge. The authors suggested a serotonergic dysfunction in SAD patients to explain these findings (Coiro et al., 1993).

In 1994 Yatham et al. from the University of British Columbia in Canada, tested this same approach (Yatham and Michalon, 1995). They recruited 10 SAD patients (6 women, 4 men) with a mean HDRS [15.8 ± 3.12], and compared with the same number of healthy controls, during winter and fall. Using the same dose of 60 mg of d-Fenfluramine as challenge, the authors found no differences between groups before and after drug administration. They suggest the small sample did not provide them sufficient power to detect small changes and that different populations (including gender differences) might be responsible for the conflicting results seen in the previous study (Yatham and Michalon, 1995).

3.5 Light Therapy

In 1995, Anna Wirz-Justice et al. from Basel, Switzerland, intended to check the effects on cortisol of 'Natural Light Treatment" (NLT), (which consisted in a 1-hour morning walk outdoors) vs 'Artificial Light Treatment' (ALT), in SAD patients (Wirz-Justice et al., 1996). From a total of 74 SAD patients, 34 participated in the study and 28 finished the protocol. Participants were divided into 2 groups, according to their own preference [20 NLT (mean HDRS = 18) vs 8 ALT (mean HDRS = 20)]. They were followed weekly with depression scales and had sleep and food logs filled daily. They also provided saliva samples for cortisol assessments and rated their humour based on a visual scale. At baseline, there was no difference in hormone levels between groups. After one week, participants exposed to natural light had a significant improvement in depressive symptoms (reduction of 65% on HAMD) compared to artificial light. In addition, cortisol levels were significantly lowered in this group and tended to return to baseline values after the withdrawal of treatment. Participants on the natural light group were also found to have an advanced mean wake up time (by 40 minutes), an advance sleep midpoint (by 26 minutes) and spent, on average, 30 minutes less in bed. Natural light was also shown to reduce carbohydrate craving in the second part of the afternoon. The authors suggest this effect is mainly due to light, suggesting that exercise was limited to walking, and so had minimal effect. They emphasize the need for walks in winter as a means of reducing SAD symptoms.

In 1996 Rosenthal's group aimed to evaluate the effects of 9 days of ALT in 22 depressive patients with a seasonal pattern (including 10 participants with a BD type II

diagnosis, and 1 participant with BD type I), compared to 24 healthy controls. The aim was to investigate the consequences of LT in the hormonal profile of SAD patients. They found that patients had a significant symptomatic improvement with light therapy (HAMD off LT=19, after LT=8; < 0.01). However, they found no differences in cortisol levels (at baseline and after treatment) between the two groups. The authors suggest that measures of free cortisol would be more specific, something they were not able to do (Oren et al., 1996).

After this, Thalen et al., from the Karolinska Institute in Stockholm, Sweden, were able to recruit a larger sample of SAD patients (Kjellman, 1997). In 1997, they recruited 63 depressed patients, 42 with a seasonal pattern (35 women) vs 21 (16 women) without a seasonal pattern. Participants were divided into two arms: morning and night light therapy. At baseline, levels of hormones were the same between groups. They found that LT had a bigger effect in symptomatic improvement in SAD patients compared to depressed controls without seasonal pattern (50% vs 21% reduction on depressive scores; $p < 0.01$), regardless of the time of administration. Also, there was a small but significant correlation with symptomatic improvement and an advancement of cortisol nadir (1 hour delay = - 4.5 % change in depression scale; $p < 0.05$), which was larger in participants receiving light in the morning ($F_{159} = 12,74$; $p < 0.01$) (Kjellman, 1997). The study also found that SAD participants reported significantly more frequent carbohydrate craving than non-seasonal depressed individuals, although this was not correlated with hormonal levels.

Also in 1997, Avery et al. recruited 12 SAD patients and 9 controls, but only 6 (all female) patients with SAD and 6 controls finished the study (Avery et al., 1997). The study measured baseline cortisol levels and rectal temperature during an overnight hospital admission. After that, participants underwent 2 hours of light therapy at home, in the morning time, for 4 weeks. They were then readmitted to repeat the protocol. SAD patients were found to have phase delays of the minimum temperature (5:42 AM vs 3:16 AM; $p < 0.01$) and a delayed cortisol nadir (12:11 AM vs 11:38 PM in controls; $p < 0.05$). No other statistically significant difference was seen between groups. After LT, there were no significant changes, although a trend for chronologic adjustment was seen (from 5:42 AM to 3:36 AM for lowest temperature; and from 12:11AM to 11:38 PM for cortisol nadir; $p = 0.06$).

3.6: Light Therapy + meta-chlorophenilpiperazine (m-CPP) (5HT agonist) challenge

In 1997, Schwartz and colleagues investigated the effects on temperature, cortisol measures and reactions to the infusion of another 5HTa, in this case, *meta*-chlorophenilpiperazine (m-CPP). They were following one of their own leads that showed behavioural activation after m-CPP in SAD patients (Joseph-Vanderpool et al., 1993). Researchers recruited 17 patients with SAD (3 men) and 15 controls (3 men) during winter. All subjects underwent 2 phases of "treatment": 3 weeks of LT + 3 weeks of "untreated condition" (which involved less exposure to natural light and the use of dark goggles with 3% light, while outdoors on sunny days). The order was randomized. On the third week, participants were admitted overnight for infusion tests (either 0.8 mg/kg of m-CPP or placebo) and had hormonal levels assessed.

Baseline measures showed a trend for higher cortisol in SAD patients compared to untreated controls and compared to themselves after LT. After the m-CPP challenge, they found that patients with SAD had a blunted ACTH response compared to controls (drug x time x group: $F_{(6,138)} = 6.39$; $p < 0.01$), but there was no difference in cortisol levels between groups (Deegan et al., 2009). They suggested a serotonergic dysfunction as a plausible mechanism in SAD pathophysiology. They also found a reduction of temperature at night in the light treated group, which was weakly associated with symptomatic improvement.

The results from Schwartz encouraged more research with this 5HTa compound, and in 1998, Levitan et al. in Canada used the same m-CPP challenge in 14 SAD patients (all women) and 15 healthy matched controls (Article, 2008). At baseline, cortisol levels between groups were the same. Patients were then admitted overnight and in the morning received a lower dose of m-CPP (0.1mg/kg) than in Schwartz's study. Although participants with SAD described mood improvement after the infusion, there was no significant difference in cortisol levels between groups. The authors suggest that more specific serotonergic agonists could improve our understanding of the role of serotonin and HPA axis in SAD. However, due to heterogeneous methods and populations, the study did not replicate the previous findings.

3.7: Cortisol Awakening Response (CAR)

In 2011, Thorn et al. (Thorn et al., 2011), in London, measured the Cortisol Awakening Response (CAR) and the diurnal pattern of cortisol secretion of 26 patients with self-assessed SAD (recruited from the local Seasonal Affective Disorder Association [SADA- UK]) and compared them to 26 healthy matched controls. Participants collected their own salivary

cortisol samples throughout the day, for 2 consecutive days, during summer and winter. They were supposed to collect samples on awakening and 15, 30 and 45 minutes after; and then after 3, 6, 9 and 12 hours. This was to distinguish the CAR from the remaining cortisol diurnal profile. Subjects were also asked to fill several psychological measures, including how long they expected to be busy in the next day, the Stress Arousal Checklist (Cox and Mackay, 1985), the Seasonal Pattern Assessment Questionnaire (Mersch et al., 2004), the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983), and the 14-item Perceived Stress Scale (Cohen et al., 1983). The authors grouped some of these scores to develop a "distress" construct and an "arousal" one. The results of the study show that there were no differences between SAD and control groups during summer in either hormones or psychological distress. However, in winter, SAD patients had a significant attenuated CAR in comparison to healthy control participants ($F_{(1.9,97.3)}$ = 75.91, $p < 0.01$). Importantly, there was a significant three-way interaction between season, sample and group ($F_{(F=2,100)}$ = 4.5, p = 0.01). In winter, the CAR was significantly attenuated in SAD participants in comparison to controls. This three-way interaction accounted for a significant main effect of season ($F_{(1,50)}$ = 5.662, p = 0.02) and a significant two-way interaction between sample and group ($F_{(1.9,94.1)}$ = 3.159, p = 0.05). The "dysphoria" construct was found to be inversely correlated with CAR levels during winter, but not in summer (p=0.03). Interestingly, there was no difference between groups on circadian variation. The authors suggest that it can be ignored in future research since the CAR is under a different regulation from the remaining diurnal cortisol profile (Clow et al., 2010).

4- Discussion:

To our knowledge, this is the first review to systematically evaluate and summarize the different approaches used to investigate HPA axis function in SAD. Our results show that findings are inconsistent, mainly due to different methods and heterogeneous populations. Most (if not all) studies did not have enough statistical power to detect small hormonal differences between groups. Studies followed an interesting chronology, learning from previous scenarios. Methods included hourly rectal temperature measures, overnight admissions, blood sampling throughout 24 hours with venepunctures and the use of dark-goggles in participants in off-light groups. These methods do not provide optimal conditions to study stress-related physiology since they carry a good amount of stress themselves. Technological advances (and greater accessibility to them), enabled researchers to perform the

most rigorous (and simplest) study so far, with salivary cortisol measures taken at home (providing a more realistic setting for a stress-related study) demonstrating an attenuated cortisol awakening response in SAD participants during winter, but not in summer (Thorn et al., 2011).

The cortisol awakening response is subject to a different regulation mechanism compared to the circadian cortisol profile (Clow et al., 2010; Thorn et al., 2009). The CAR is the rapid increase in cortisol levels following morning awakening and it seems to be regulated not only by HPA axis activation but by a SCN extra-pituitary neural pathway, that sends signals directly to the adrenal glands in order to sensitize receptors before ACTH stimuli (Thorn et al., 2009). Depending on this sympathetic mechanism, the adrenal might become more or less sensitive to ACTH, consequently altering cortisol release (Clow et al., 2010). The hippocampus has been hypothesized to play a major role in this task (Fries et al., 2009). This physiological mechanism may be affected by several factors, including adverse prior day experiences, boosting this function to provide extra energy for imminent demands (Adam et al., 2006). It may be that diminished light input in the SCN disrupts this extra-pituitary mechanism, leading to the attenuated CAR response that we see in SAD patients during winter (Thorn et al., 2009). This agrees with the finding of delayed ACTH and cortisol release after oCRH challenge performed by Rosenthal's group. They hypothesized a dysfunctional CRH system, but sympathetic activity and consequent adrenal sensitivity might play an important role (Joseph-Vanderpool et al., 1991). Consistently, SAD individuals were found to have lower levels of α-amylase, a possible marker of low sympathetic tone (Ivanova et al., 2017).

Both studies of DST in SAD participants found that the majority of patients have normal suppression after 1mg of Dexamethasone (James et al., 1986). Their samples were small, heterogeneous and 10% of patients did not, in fact, suppress cortisol after the challenge. In both studies, sample bias, especially due to gender differences, confound the results. Gender plays a major role in HPA axis regulation and SAD incidence (80% female) (Koch et al., 2017). Gonadal steroids differently impact HPA axis function (Le Tissier et al., 2016). While, testosterone generally tends to inhibit stress reactivity (Viau and Meaney, 1996), estradiol appears to enhance it, possibly by increasing adrenal sensitivity to ACTH (Figueiredo et al., 2007). One study using salivary cortisol measures found that women with depressive symptoms in their premenstrual period tended to have lower cortisol levels compared to themselves after menstruation (Odber et al., 1998). Cyclic fluctuations of estradiol seen in women of reproductive age, and their consequent modulation of adrenal sensitivity, may play a role in the increased vulnerability of women to develop stress-related conditions (Weiss et al., 1999). This

study provides evidence for an interesting concept, the one of "relative hypocortisolism". When compared to controls, normal cortisol levels do not necessarily mean sufficient cortisol signalling for the individual. Longitudinal studies using patients as their controls might provide key insights into this.

The studies with serotonin agonists and HPA axis function in SAD were conducted with heterogeneous, small samples, and could not be replicated. Serotonin abnormalities are commonly cited as consistent findings in SAD literature (D., 2010), but no clear conclusions from serotonergic challenges can be drawn from the studies conducted so far. Serotonin systems show bidirectional interactions with the HPA axis (Mario F. Juruena et al., 2017) and play an important role in circadian rhythms, partially by modulating the SCN response to light (Ciarleglio et al., 2011). However, their impact on HPA function in SAD is still to be elucidated. Future studies might aim for multiple cortisol salivary measures at home before, during and after long periods of treatment with serotonergic drugs, observing the possible impact of these drugs in cortisol release and rhythms at an individual levels.

The studies with light therapy in SAD related to HPA axis function were also conducted with heterogeneous methods and populations. Virtually all of them found symptomatic improvements in the SAD population, but their analysis of HPA axis function was conflicting and inconclusive. Only one study was positive and suggested a decrease in cortisol levels after intervention (morning walk – natural light). This study has several potential confounders, such as high attrition, patient preference (i.e. non-randomized), physical activity, social interaction and depression severity (Wirz-Justice et al., 1996). Cortisol levels tended to get back to usual values after withdrawing of the strategy. Recent studies have shown that light might play an important role in the treatment of seasonal and non-seasonal depression (Perera et al., 2016; Schwartz and Olds, 2015), mainly by modulating circadian rhythms. Evidence suggests that humans (as most mammals) are vulnerable to the manipulation of light cues, entraining circadian rhythms accordingly (Wehr et al., 2007). Using this theoretical background, chronotherapeutic strategies are increasingly under scrutiny as possible treatments for mood and metabolic disorders (Coogan and Thome, 2011; Dyar and Eckel-Mahan, 2017; Schwartz and Olds, 2015). Light seems to play an important role in energy regulation and symptomatic improvement in SAD, but their relation to HPA axis modulation is still unclear.

5- Conclusion:

Based on the findings of this systematic review, we conclude that there is still insufficient evidence to classify SAD as a hypocortisolemic condition when compared to controls. Methodological inconsistencies, very small sample sizes, and different populations did not allow for replication of results. Our findings are consistent with a recent systematic review that failed to show cortisol abnormalities in atypical depression (the typical seasonal pattern) when compared to melancholic depression (Mario F Juruena et al., 2017). As those authors, we suggest a future focus on clinical characteristics, especially neurovegetative symptoms, might provide a deeper understanding of the biological mechanisms involved. So far, the most notable finding in the field is the attenuated cortisol awakening response seen in winter, but not in summer, demonstrated in SAD patients.

Future research on SAD and HPA axis might focus on salivary assays, which measure a more reliable, "free", biologically active form of cortisol. This method also allows patients to collect the sample themselves, at home, reflecting more natural conditions, a crucial factor in stress-related studies. Furthermore, it is now possible to track subjects regarding mood rating, eating and sleeping patterns, as well as to obtain physical data (e.g. heart rate, heart rate variability) via ecological momentary assessement using smartphones, smartwatches or actigraph apps. Because cortisol seems to impact most of these functions, including sleep (Vadivelu et al., 2016), these data can be correlated with biochemical (possibly salivary) findings before, during and after mood episodes (in this case, SAD) subsides. Following patients prospectively for longer periods (years) could also give us estimates of "relative cortisol deficiency", comparing patients as their own controls (Celec et al., 2009; Odber et al., 1998). Another possible approach would be to follow patients in both hemispheres and see if these immune-endocrine patterns are consistently inversely correlated, as a recent paper suggests (Dopico et al., 2015).

There is strong evidence for seasonal variation in a myriad of human psychological features (from mood and cognition to genetic expression (Abbasi, 2018; Byrne et al., 2015; Geoffroy et al., 2015; Lowell and Davis, 2008)), and seasonality clearly impacts the lives of (at least) one sub-group of people with mood disorders. Regardless of the classification status of SAD (BD or recurrent MDD), the presence of seasonality might provide the perfect condition to study physiological changes in depressive disorders. Its high predictability provides a clear opportunity to study these changes during the whole process and the technology now available enables us to have a variety of physical and activity data to correlate with these changes.

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Table 1: Seasonal affective disorder and HPA axis studies:

Author/ Year	Sample	Diagnostic tools	Outcome measures	Key findings	Limitations
Rosenthal N et al. 1984	7 cases. No controls.	2 years of winter depression, by RDC	DST	Normal suppression. No difference between summer/winter.	Small n. 1st study did not describe the methods of DST. No control group.
James SP, Rosenthal N et al. 1986	20 cases. No control group.	RDC, SPAQ, HRSD-21 (>14)	DST	Normal suppression in 18 patients; 2 non-suppressors	Small sample. No control.
Jacobsen FM, Rosenthal N, et al. 1987.	10 cases; 10 healthy matched controls	RDC, 2 years of the seasonal pattern	HDRS + 7 item atypical symptoms; Blood Cortisol, Melatonin and Prolactin levels, after 200mg of 5-HTP.	Baseline prolactin levels greater in the SAD group ($p<0.02$); trend for higher basal cortisol levels in the SAD group ($p=0.09$); no statistically significant differences between groups after 5-HTP.	Small sample.
Joseph-Vanderpool JR, Rosenthal N et al. 1991.	10 cases, before and after light therapy (5 male); 13 matched controls.	DSM III R criteria (SCID); HRSD-21 (>14)	HRSD; Blood ACTH, cortisol levels (basal and after ovine CRH stimulation)	Baseline cortisol levels lower in SAD patients ($p=0.02$); after oCRH, SAD patients had	Small sample. Not representative of real-world conditions (F>M).

				delayed and reduced responses in ACTH ($p<0.02$) and cortisol ($p<0.01$). Significant improvement in hormonal response after 9 days of LT, accompanying symptomatic improvement.	
Coiro, V et al., 1993.	7 (5 male); 8 healthy controls (6 male)	SCID for DSM III R with a seasonal pattern. HDRS-21.	Blood Cortisol and Prolactin levels after 60mg of d, Fenfluramine (5-HT agonist) and placebo, in winter and summer	Prolactin ($p<0.02$) and cortisol ($p<0.05$) levels significantly lower in the SAD group after dF. Combined ($p<0.02$);	Small sample, composed mainly by males.
Yatham, LN. 1994	10 (6 female); 10 healthy matched controls	SCID for DSM III R; SPAQ. HDRS-21.	Blood cortisol and prolactin levels after 60mg of d, Fenfluramine or placebo	No significant difference between groups	Small sample, different from previous study
Wirz-Justice et al. 1995.	28 cases (26 female); Same group after intervention: 20 (19 female) natural light; 8 (7 female) artificial light	HDRS-21, at winter	HAM-D, CGI, food and sleep log, salivary cortisol and melatonin	Symptomatic improvement in the NL group (d=2.17); Morning cortisol significantly lower in the natural light group ($p=0.04$), return to baseline after withdrawal. Melatonin changes not statistically significant. Less carbohydrate craving after natural light	Physical activity in the natural light group might be a confounder
Oren, DA, Rosenthal N, et al. 1996.	21 cases (10 BD2, 1 BD1); 8 males; 20 controls	SPAQ; HRSD-21 (>14), atypical depression scale (ATY)	Blood cortisol, prolactin, thyrotropin. HRSD	Cortisol levels did not differ between SAD (before and after LT), and controls	Heterogeneous sample

Thalen, B-E, et al. 1997	42 SAD (35 female); 21 non-seasonal depression (16 female)	DSM III criteria; Comprehensive Psychological Rating Scale (CPRS)	HRSD-18; Serum cortisol and melatonin levels	No difference in baseline hormones. Light therapy improved symptoms of SAD more than non-SAD. Cortisol bathyphase advanced by morning LT.	
Avery, DH et al. 1997	12 (6 finished the study); 9 controls (6 finished)	SPAQ	Rectal temperature, Blood cortisol and TSH levels	Phase delayed circadian rhythms in the SAD group, regarding lower temperature ($p<0.05$) and lower cortisol ($p<0.06$). Light therapy advanced these rhythms.	Very small sample. Cortisol findings not statistically significant. Stressful methods might have confounded results
Schwartz, PJ. Rosenthal N. et al. 1997	17 cases (3 male); 15 healthy controls (3 male) + cases after LT	Rosenthal's criteria	HDRS, HSRS-SAD version; cortisol, prolactin, ACTH, GH, NE: basal and after stimulation with Meta-chlorophenylpiperazine (m-CPP) – 5-HT agonist	Tendency for higher cortisol ($p=0.10$) and lower NE ($p=0.07$) in SAD patients at baseline. Blunted ACTH ($p<0.05$) and NE ($p<0.05$) responses after m-CPP in the SAD group. No differences between groups in cortisol, prolactin or GH after m-CPP. Reduction of night temperature after LT in the SAD group.	Stressful methods might have confounded results
Levitan, RD et al. 1998	14 (all female); 15 healthy matched controls	SCID for DSM III with a seasonal pattern; HDRS 29 item (8 item addendum with atypical features	Prolactin and cortisol levels (baseline and after m-CPP)	No statistically significant differences in baseline levels. Positive correlation between cortisol and	

				HDRS score at baseline in SAD group (p=0.02). Blunted prolactin response in the SAD group (p=0.04)	
Thorn, L, et al.	26 (19 female); 26 healthy controls (15 female)	SPAQ, salivary cortisol, HADS, Stress arousal checklist	SPAQ, salivary cortisol, HADS, Stress arousal checklist	SAD patients had lower cortisol awakening response during winter, but not during summer, compared to controls (p<0.02). Diurnal cortisol variation was the same between groups.	

Figure 1: Light activation of HPA axis

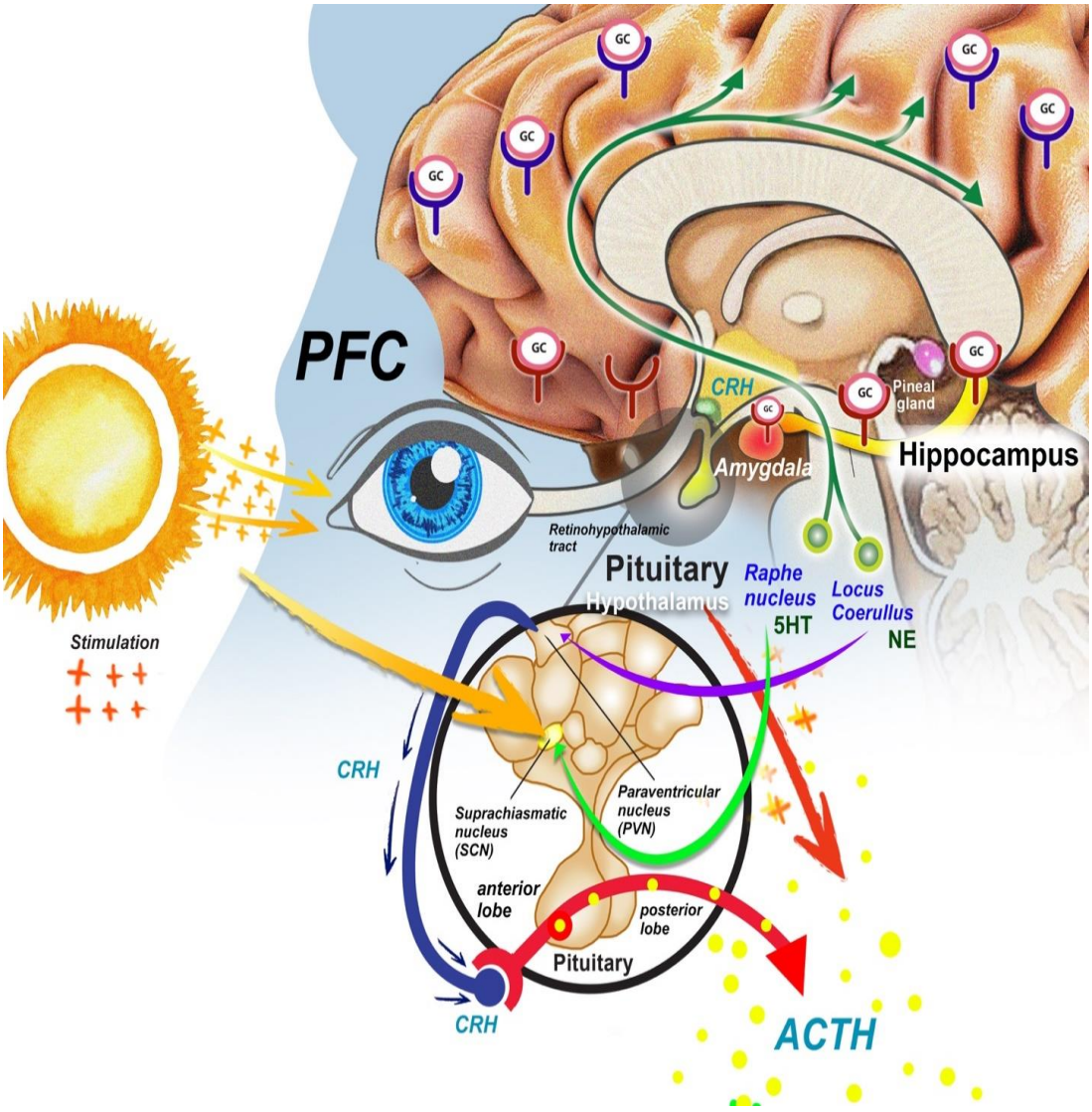

Fig 1: After light reaches photosensitive receptors in the eye, it sends a message through the Retino-Hypothalamic-Tract to the Suprachiasmatic Nucleus (SCN) of the hypothalamus. The SCN activates the Paraventricular nucleus of the hypothalamus (PVN), which liberates corticotropin-releasing hormone (CRH) and initiates HPA axis response. The final product of this process is cortisol that exerts negative feedback on mineralocorticoid receptors (MR) (Red, present in the Hippocampus, Amygdala and Prefrontal cortex) and glucocorticoid receptors (GR) (Blue, expressed diffusely in several brain regions). Serotonin and Norepinephrine neurons have important connections with the SCN and the PVN, respectively.

Figure 2: Epigenetic properties of cortisol

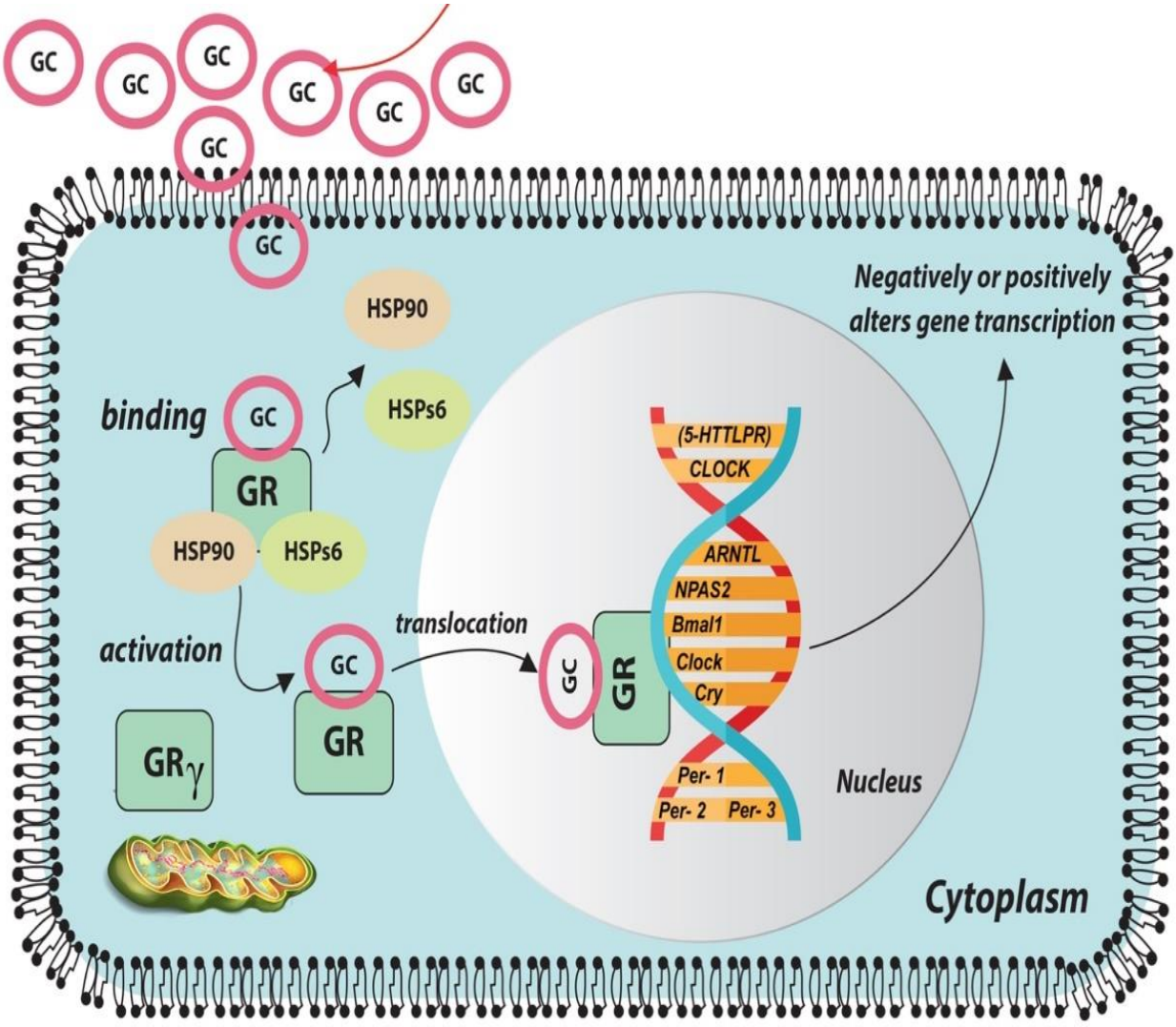

Fig 2: Glucocorticoid receptors (GR) are present in almost every tissue of the human body. Cortisol has facilitated passage through the cell membrane and GR's are localized inside the cytoplasm, along with heatshock proteins. After cortisol (GC) connects to GR, the complex is transported to the cell nucleus, where it partially regulates genetic expression. GC also appear to exert its effects directly in the cell mitochondria.