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Predictability of seasonal mood fluctuations based on electroencephalographic biomarkers and cognitive vulnerabilities in a non-clinical sample

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Útdráttur

Spá um árstíðabundnar sveiflur á líðan sem er byggð á heilalínuritum (EEG) og hugrænum kvillum úr ó-klínísku úrtaki

Bakgrunnur: Með minnkandi dagsbirtu gæti fólk verið útsett fyrir áhrifum árstíðarbundinna skapsveiflna og þjást af lítilli orku, fólk gæti haft lítinn áhuga á athöfnum, upplifað þyngdarbreytingar, svefnleysi, einbeitingarörðugleika, þunglyndi og sjálfsvígshugsanir. Fáar rannsóknir hafa verið gerðar í leit að líffræðilegum ummerkjum árstíðarbundinna skapsveiflna í heilanum, eins og með EEG mælingum (heilalínuritum).

Markmið: Markmið þessarar rannsóknar var að ákvarða hvort hugrænir veikleikar, eða lífvísar heilalínurita af heilastarfsemi, eða notkun þeirra beggja saman, hentar betur til að spá fyrir um árstíðabundnar sveiflur á líðan einstaklinga, byggt á mati sem var framkvæmt yfir sumarið árið á undan.

Aðferðir: Að sumri til var úrtak 68 þátttakenda rannsakað með spurningalistum og heilalínuriti. Að vetri til var framhaldskönnun skráð og þátttakendur flokkaðir í hóp með þeim sem upplifa verulegar árstíðabundnar skapsveiflur (N = 20) og með þeim sem höfðu ekki sjálfir sagt frá þunglyndiseinkennum bæði á sumrin og yfir vetrarmánuðina. Stuðningsvektarvél (en. support vector machine) var þjálfuð í að spá fyrir um þunglyndiseinkenni á veturna, annað hvort með lífvísum heilalínurits (en. EEG biomarker) einum saman, gögnum úr spurningarkönnunum við grunnlínu (en. baseline) eingöngu, eða samblandi af þessu tvennu. Tölfræðigreiningaraðferðin Leave-one-out-fold cross validation og nested subset selection (lasso regularization) var notuð við úrvinnslu.

Niðurstöður: Nákvæmni fyrir flokkun var allt að 76,12% fyrir sálfræðilega mælingar einar og sér, 71,64% fyrir EEG/heilalínurit eingöngu, og 82,09% fyrir EEG/heilalínurit að viðbættum sálfræðilegum mælingum.

Ályktanir: Mælingarnar að sumri til með spurningalistanum voru meira óyggjandi en gögn fengin úr heilalínuriti sem framkvæmd voru til að spá fyrir um árstíðabundnar sveiflur á líðan yfir vetrarmánuðina. Það er hagkvæmt að sameina heilalínurit við vitsmunalega örvun með sálfræðilegu mati til að efla forspárgildi.

Lykilorð: árstíðabundnar skapsveiflur, skammdegisþunglyndi, vanhugsaðar hugsanir, vitrænir veikleikar, meðferð með ljós, lífvísar heilalínurits (en. EEG biomarker), spá, vélrænt nám, samtenging (en. connectivity), nákvæmni (en, accuracy)

Abstract

Induced by decreasing light, people affected by seasonal mood fluctuations may suffer from low energy, have low interest in activities, experience changes in weight, insomnia, difficulties in concentration, depression, and suicidal thoughts. Few studies have been conducted in search for biological predictors of seasonal mood fluctuations in the brain, such as EEG oscillations.

Aim: To determine whether cognitive vulnerabilities, or biomarkers of brain activity, or their combination is better suited to predict seasonal mood fluctuations, based on assessments conducted in summer.

Methods. A sample of 68 participants was examined with questionnaires and electroencephalography (EEG) in summer. In winter, a follow-up survey was recorded and participants were grouped into those with significant mood decline (N=20) and those without self-reported depressive symptoms both in summer and in winter. A support vector machine was trained to predict mood decline by either EEG biomarkers alone, questionnaire data at baseline alone, or a combination of the two. Leave-one-out-fold cross validation and nested subset selection (lasso regularization) was used.

Results. The accuracy for classification was at up to 76.12% for psychological measurements alone, 71.64% for EEG alone, and 82.09% for EEG combined with psychological measurements.

Conclusions. Summer-recordings of questionnaire data were more conclusive than EEG biomarkers for prediction of sad mood in winter, but it is advantageous to combine EEG with cognitive stimulation as well as psychological assessment to boost predictive performance.

Keywords: seasonal mood fluctuations, Seasonal affective disorder, maladaptive thoughts, cognitive vulnerabilities, exposure to light, EEG biomarkers, prediction, machine learning, connectivity, accuracy

I dedicate the thesis

to my son Sólmundur Hrafn and Heike Viktoria, their children

Eva, Alex and Leon,

to my daughter Sunneva Bernhardsdottir and Sean Kersey, and

my newborn grandson in Winnipeg, Manitoba.

Foreword

Cognitive vulnerabilities favoring seasonal depression and prediction of symptoms of seasonal mood fluctuations by biomarkers of brain activity associate at least two sciences: psychology and computer sciences. The methods of artificial intelligence enable researchers to analyse large data sets and investigate high-dimensional feature spaces. We used a machine learning algorithm to evaluate data from electroencephalography (EEG) and psychological questionnaires to identify the most promising markers for predicting seasonal mood changes.

Prognostic biomarkers taken by EEG at times without symptoms allow to predict to a certain degree the occurrence of sad mood at a later point in time - except an appropriate treatment succeeded in the meanwhile. Identification of such a population at-risk in order to inform targeted interventions in the course of the disease that prevent worsening of symptoms is a common goal of medical prognostic procedures. For this reason our project involves the electroencephalogram (EEG), which is an objective measure, additionally to self-report questionnaires, both recorded from participants in summer to identify individuals suffering from seasonal mood fluctuations in winter.

The present paper is new in many aspects by using a broad range of EEG together with questionnaires, applying artificial intelligence.

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First of all, I thank everybody for his/her participation in the study, and the BA-students at the Faculties of Psychology at the University of Akureyri Anna Hjálmveig Hannesdóttir, Elsa Huld Jensdóttir, Máni Snær Hafdísarson, Sara Teresa Jónsdóttir, Sigrún María Óskarsdóttir, and Silja Hlín Magnúsdóttir to collect the baseline data. Also my thanks to the BS-students of the Faculties of Psychology at the University of Iceland, Anton Nikolaisson Haydarly, Elena Arngrímsdóttir, Erla Ástrós Jónsdóttir, Inga Valdís Tómasdóttir, María Lovísa Breiðdal and Ólöf Traustadóttir to sample the data in the online part of the study.

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My thanks to Raimund Bernhard to support and encourage me all my life.

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1 Introduction

This study is about the predictability of seasonal mood fluctuations by cognitive vulnerabilities, electroencephalographic biomarkers and machine learning. The first chapter gives background information by highlighting scientific research results about seasonality, chronobiological and cognitive vulnerabilities, and neurophysiological biomarkers used by artificial intelligence. At the end the research questions and methods are introduced. The second chapter includes our scientific article, written for the *Journal of Affective Disorders*.

1.1 THE THEME

In the year 2020 up to 350 million individuals would be affected by depression worldwide, as estimated by the World Health Organisation (GBD, 2017). The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (American Psychiatric Association, 2013) identified one disease type of depression - associated to seasonality - as Major Depressive Disorder (MDD) with Seasonal Pattern, therefore called Seasonal Affective Disorder (SAD), meeting the following criteria: the individual experienced the last two years two or more episodes of depression, occurring and disappearing with full remission at a specific time of the year. Additionally to depressive symptoms - in contrast to MMD - changes in appetite, craving for carbohydrates and hypersomnia can be present (Rosenthal et al., 1984). In this article we discuss mild seasonal mood changes, mostly referring to the winter pattern of SAD, as well as clinical research results of depression.

Definitions of key terms

accuracy: the proportion of correctly classified samples

attributional style: the tendency how to explain the cause of an positive or negative event

biomarker: a changed physiological factor, often attached to a disorder

habitual behaviours: automatic, more difficult to control, associated with lack of intent and awareness when it start

ruminating: increased negative mood response, no longer motivated by goals

rumination: a goal-directed activity, thinking obsessionally

sensitivity: accuracy to participants who would experience sad mood in winter

support vector machine: classification model in machine learning

Prevalence of seasonal mood fluctuations

Up to 3% of the world population is said to suffer from SAD (Majrashi et al., 2020). Both variations of SAD are present, the summer and winter type, though to a different extent. Among 2,819 participants in the Netherlands, 3% were suffering from winter SAD, and 0.1% of sad mood during winter, according to assessment with the Seasonal Pattern Assessment Questionnaire (SPAQ, Murray, 2003) (Mersch et al. 1995). The winter subtype experiences depressed mood every year in fall and winter,, and symptoms go back with the rising sun again (Rosenthal et al., 1984; 1985). An Icelandic study with 410 participants at the age of 18 to 59 years found that seasonal mood fluctuations occur more frequently among younger people than older individuals (Höller et al., 2021). Moreover, women are four to five times more likely to experience SAD (Mersch et al., 1995; Wirz-Justice et al., 2019).

The winter subtype is a common disorder in general populations, Magnusson (2000) stated in a study. Brainard et al. (2008) reported a prevalence of around 10% in Scandinavia, which was rejected in the case of Icelanders by Magnusson et al. (2000), Oskarsson (1988) and Magnússon & Stefánsson (1993), who measured a relatively low rate (3.8%) compared to other Nordic countries.

Descendants of Icelandic emigrants in Canada have been repeatedly participants in research studies (Magnússon & Axelsson, 1993). In a controlled study, the results of the self assessed SPAQ by 204 Icelandic descent inhabitants of Winnipeg in Manitoba showed a lower prevalence of SAD among them as compared to Canadians without Icelandic roots (Axelsson et al., 2002b). A *light versus climate* dispute broke out over whether Icelanders have already genetically adapted to the reduced natural daylight availability in the darkest seasons (Axelsson et al., 2002a; 2002b; Michalak & Lam, 2002). Subsequently the results of the long term Zurich cohort study with 499 Sviss participants found a prevalence rate of 7.52% suffering from seasonality, and a rate of 9.96% for MDD with a single depressive episode in winter (Wirz-Justice et al., 2019).

Diagnosis and treatment

To diagnose depression generally, physical exams and laboratory tests belong to the tools practitioners and health care staff use to perform a differential diagnosis and to exclude other reasons for the disease. Doctors ask about the biological and psychological symptoms. Helpful to specify the diagnosis of depression are questionnaires as the first step, when an appointment with psychologists, psychiatrists or other mental health professionals is not available immediately to perform a clinical interview. Already in the early scientific discussion of seasonal mood fluctuations Blacker,

Thomas and Thompson (1997) screened 2,225 inhabitants of London about seasonality, and found in 196 depressive participants a varying incidence and recovery of major and minor depressive episodes, depending on how severe the disease was. In major depression the peak of incidence occurred in December to February, but in summer months for minor depression. Additionally, biological variables are important for the onset of depressive episodes, for example physical illness and recurrence, bipolarity, family history, and endogeneity. In the case that the self-reported description of the symptoms matches the criteria of SAD, the SPAQ is commonly used.

Treatment

Searching for the reasons why people develop a sad mood in fall and winter, and to have a chance to prevent the disease, it may be helpful to look at the opportunities of a successful treatment method. The fact that symptoms appear annually at the same season suggest that they are triggered by the exposure of light.

It is recommended to choose effective treatment when managing depression according to the individual patient's preferences (Baskaran et al., 2012; Kurlansik & Ibay, 2012). As exposure to light as a biological mechanism provides one explanation for the occurrence of sad mood in the dark season, light treatment is proposed as a therapy, possibly also because light exposure seems to be an easy-to-be controlled factor among environmental conditions that change with season (Brainard et al., 2008).

Antidepressants, psychological interventions, the use of agomelatine and melatonin, and light therapy are the commonly treatments for SAD, as a update of the Cochrane reviews showed (Forneris et al., 2019; Gartlehner et al., 2019; Nussbaumer-Streit et al., 2019a; 2019b). Lifestyle changes and a vitamin D food

additive as preventive interventions are mentioned additionally to antidepressants, light and psychotherapies (Melrose, 2015; Nussbaumer et al., 2017; 2018).

The long-term advantages of Cognitive Behavior Therapy (CBT) over light therapy in winter was of further scientific interest. Rohan et al. (2016) studied the advances of CBT, compared to light therapy. These findings were examined more closely by Camuso and Rohan (2020). The aim of their study was to discover criteria in the self-report questionnaire data, which allow to decide the right treatment type that matches appropriately with the patient's profile. Therefore, the chronobiological and cognitive vulnerabilities of 177 patients diagnosed with SAD were assessed. After a six weeks long treatment by light or CBT the researchers found out that the morning chronotype experienced an improvement regarding their depressive state. Another result of a cohort study regarding remission of SAD symptoms was that a decade after diagnosis of SAD only 27% of the participants would still be categorised as SAD cases (Cléry-Melin et al., 2018). Sitnikov et al. (2013) suggested that individuals suffering from serious seasonality symptoms should be treated by combining light treatment and CBT, because the application of one at once resulted in lower response than to use both together. Knapen et al. (2014) discovered by a self-report questionnaire that 83 participating women expected more recovery by therapy than men (25 participants).

Vulnerabilities and seasonal mood changes

Two vulnerabilities, described by Young et al. (1991), are the biological and as well as the psychological factor, both interacting in individuals with SAD. The Dual Vulnerability Model was based on the observation that depressions fluctuate temporally. Individuals with seasonal depression experience times

weakly affected by the disease or being without symptoms, changing with episodes of depression. The chronic disorder is more or less present at all times. Negative appraisal of vegative changes due to biological vulnerabilities cause cognitive conditions, which both work together to develop SAD (Meyer & Young, 2015).

In the case of seasonal mood fluctuations this fact allows us to research the disorder in times without episodes, for example the winter depression in summer. The Dual Vulnerability Model was specified when Rohan et al. (2019) found that maladaptive thoughts and behaviors belong to the psychological vulnerabilities inherent to individuals suffering from seasonal mood fluctuations. Finding maladaptive thoughts in individuals without other physiological symptoms in summer allows the prediction of SAD before episode onset in fall or winter happens. In the following, vulnerabilities that might be detectable in summer are presented in more detail.

Chronobiological vulnerabilities

The phenomenology of SAD, for example symptoms distinguishing it from MDD, the seasonal recurrence in spring and summer, and the response to light and cognitive behavioral therapy, highlight the dual vulnerable character of SAD, where genetics, circadian rhythm, and neurotransmitters may play a role as the person´s chronobiological vulnerabilities (Sohn & Lam, 2005).

Regarding biological rhythm, evening people might experience seasonal mood fluctuations more than individuals belonging to the morning orientated chronotype group. Salehinejad et al. (2021) assume a difference in genetic, physiological, and behavioral nature between morning and evening persons, which affect cognition and brain functions. In their study, working memory and attention were tested in 32 participants. The authors concluded that

chronotype influences higher order cognition, behavior as well as physiological mechanisms.

The fact that the degree of exposure to light seems to be a trigger for seasonal changes led to the suggestions that melatonin could be responsible for seasonal physiological changes.. Arendt (2012) studied melatonin treatment and its relationship to light, and discovered that it is also the reason why light therapy aims at deceiving people's perception about nature: increased exposure to artificial light sources would normalize the melatonin household, eventually making them feel better.

Evening chronotypes suffer from sleep disturbances. Sleepiness measured by EEG in 16 female participants with SAD showed a similar EEG like evening chronotype, and 0.5mg administered melatonin treatment in the evening did not affect their sleep patterns, but sleep deprivation improved the sleep build-up (Danilenko & Putilov, 2005). It is also known that sleep disturbances occur specifically with SAD (Tonetti et al., 2014). Wirz-Justice (2018) made suggestions for light treatment to support people´s recovery with other mental disorders, general health, and well being, because light exposure influences physiological processes, for example gene expression and hormones.

Cognitive vulnerabilities

Rohan et al. (2011) studied the association of seasonality and cognitive vulnerabilities, using the SPAQ, the 88 participants were divided into groups of different degrees of seasonality: moderate, mild, and low seasonality. The psychological factors which cause people's vulnerabilities to develop and maintain SAD were evaluated by questionnaires to measure maladaptive cognitions, both in winter and non-winter seasons (spring and fall). According to their results during winter, all groups ruminate more, show more automatic

thoughts, and increased scores about light availability of the light-specific Implicit Associations Test (IAT). Participants with moderate seasonality show more rumination and negative automatic thoughts compared to the other groups. Additionally, participants with moderate and mild seasonality demonstrate poorly adapting dysfunctional attitudes than the control group.

Jensen et al. (2016) studied patients diagnosed with SAD, whether the affective recall in a verbal memory test changed with seasons. The researchers found that the recall of positive words decreased in this group in autumn and winter, and there was an inverse association between the recall of positive words and depression.

Limiting the efficacy of psychological therapies belong to the possible negative consequences of rumination (Watkins & Roberts, 2020). Regarding the future estimation, in a controlled investigation by Dalgleish et al. (2010), individuals with SAD were found to believe that negative events may happen to them, and also to other people. This has to be understood against the background that dysfunctional attitudes and automatic thoughts are more common among individuals with SAD than among people not suffering from any depression, as the research of Hodges and Marks (1998) showed. The investigators used the Automatic Thoughts Questionnaire and Dysfunctional Assumption Scale to assess cognitive vulnerabilities in ten individuals with SAD, and eleven persons depressed all year round, and found no difference between both groups. This result was replicated by Levitan et al. (1998), when the negative attributional style of 26 persons with SAD and 30 participants of all time depressed persons was compared. The association between negative thoughts and rumination in depressed people was assessed by self-report questionnaires. A study by Enggasser and Young (2007), found that ruminative

response and internal attributional style are responsible for increased sad mood and cognitive depression symptoms of the participants.

The habit-goal framework bases on the habit, when an individual is going to be controlled by negative thoughts, and depressive rumination is caused and will cause stress for the individual itself, the effects of serious depression symptoms undermines social contacts (Nolen-Hoeksema et al., 2008). The cognitive mechanism acts without being conscious, previously set goals are not achieved and a spiral of depressive episodes develops. This approach of depressive rumination, intervened by Watkins & Nolen-Hoeksema (2014), was tested by Ólafsson et al. (2020). Twenty former depressed female participants showed a higher level in automatic rumination than the control group, confirming the effect of negative thinking (Ólafsson et al., 2020).

Biomarkers

The problem of the subjectivity of self-report psychological assessments could be reduced by incorporating neurophysiological measurements (for example EEG) in order to guarantee scientific evidence generated by neuroscience data (Mumtaz et al., 2018).

Neurophysiological biomarkers

EEG is a cheap diagnostic test with high resolution that records the electrical activity of the brain by an electrode cup, which is set on the scalp. Functional Magnetic Resonance Imaging (fMRI), Magnetoencephalography (MEG), or Optical Brain Imaging (fNIR) are other diagnostic techniques competing with EEG. Additionally EEG has the advantage of easy data collection (Freeman & Quiroga, 2012), and has been used to predict treatment response, or the progression of dementia (Al-Qazzaz et al., 2014).

EEG signals allow conclusions about the brain activities beneath the scalp. In depression, functional changes in the cognitive control network occur (Otte et al., 2016). An EEG investigation by Ding et al. (2019) with 144 young adults diagnosed with MDD showed the involvement of prefrontal brain area in depressive individuals. Ferdek et al. (2016) succeeded to localize with the EEG the state of depressive rumination in the brain of 26 participants. They found a decreased information flow to the left temporal lobe from the left dorsolateral prefrontal cortex during rumination.

Passynkova and Volf (2001) combined the findings of Rosenthal et al. (1984, 1985) with earlier scientific results about cerebral hemispheric activities in depressed people, who showed a hemispheric asymmetry without suffering from symptoms (Henriques & Davidson, 1990). Passynkova and Volf (2001) suggested in their controlled study with 31 SAD patients that depressed and remitted states in individuals with SAD result in hemispheric differences, measurable by the EEG.

Participants with SAD showed an asymmetry of spectral EEG-power in frontal and parieto-temporal networks, and lower activity in frequency bands delta (0-4 Hz), theta (4-8 Hz), and alpha (8-13 Hz) compared to controls. Interestingly, the remission by seasonal change or treatment of light exposure let the hemispheric asymmetry of the lateral frontal areas appear to be normal. Volf and Passynkova (2002) concluded from this research that the brain activities, measured by EEG, give information about different depressive disorders, especially in SAD during depressed episodes and remitted stage in summer (Volf & Passynkova, 2002).

To measure depression with EEG biomarkers researchers can choose between studying people at rest or while they are showing their unfavorable thought patterns. Measuring brain activity while people are engaging in

unfavorable thought patterns results in values different from those of people who are with this vulnerability. Grin-Yatsenko et al. (2010) compared the EEG parameters of mild depressive disorder with healthy individuals during open and closed eyes resting states. Both conditions showed in participants with depression increased spectrum power in theta, alpha and beta (13-30 Hz) frequency bands at occipital and parietal sites. The authors interpreted the increased activity in theta and alpha frequencies as a decrease in activation in these cortical regions, and beta power changes were suggested to play a role in depression onset.

Analysis of large data sets

Various systems in nature, technology and in social life are based on complex networks (Sporns et al., 2004). Focusing on the interactions of the brain, three types of connections are conceptualized: structural (anatomical), functional and effective (Friston, 2011). They can be used to classify measures of connectivity of neural systems. The construction of structural and functional connectivity is based on the neural architecture, where white matter tracts connect intra- and interareal different cortical populations and brain regions (Sporns & Zwi, 2004). Structural connectivity refers to the physical architecture, where inside the „*neuroanatomical substrate*“ (Sporns et al., 2004) neurons and neuronal populations communicate in non-linear patterns, and where these activities show the neural dependence of the respective brain areas (functional connectivity). Covariation is shown as a function of frequency (Sakkalis, 2011). Finally, causal neural interaction of the brain network is interpreted as effective connectivity.

Large neurophysiological data sets of structural and functional patterns, as measured via EEG, call for a complex network analysis. Graph theoretic-based

biomarkers measure connectivity by the degree and similarity, density and rentian scaling, clustering and community structure, assortativity and core structure, paths and distances, efficiency and diffusion, centrality, and motifs and self-similarity (Rubinov & Sporns, 2010; Sakkalis, 2011).

EEG has been used to collect data for prediction of the expected acceptance of a treatment or development of a disease. Alhaj, Wisniewski and McAllister-Williams (2011) discussed the possibility to use the EEG in two ways: First, to get data about abnormal neural activity in depression, and second, to predict the likelihood of response to antidepressant drug treatment. Concerning diagnosing depression, the authors discussed EEG alpha power, alpha hemispheric asymmetry, loudness dependency of auditory evoked potentials (LDAEPs), and the combination of band-power and ERP parameters, by measuring the baseline of EEG alpha and theta power in the anterior cingulate cortex, alpha asymmetry, and the loudness dependency of auditory evoked potentials slope. The authors suggested that diagnostic accuracy can be improved by incorporating EEG measures. A comparable topic was studied in a review of 44 articles by Kaiser et al. (2018) with the result that the reviewed articles lacked information about gender, age, handedness and comorbidity, so generally disagreement was about the results regarding alpha asymmetry, measured by EEG in depressed people.

The method of measuring functional connectivity to diagnose MDD has proven to be practicable. Event-related potentials (ERPs) measure the electrical activity of the brain when people respond to stimuli, when they are asked to perform tasks or to respond to sensory stimulation, for example selecting objects, the Stroop test, answering a test, feeling well or sad, ruminating thoughts, or simply having the eyes open or closed (Baskaran et al., 2012).

Biomarkers like EEG and ERP were used in a research by Mumtaz et al. (2015), mentioning the challenge to reduce antidepressant use in patients. The following investigation studied how to classify 63 individuals into a depression or healthy group by a machine learning scheme using logistic regression, support vector machine, Naïve Bayesian, and cross validation (k=10) (Mumtaz et al., 2018). The investigators tested accuracy, sensitivity and specificity. A year later the team around Mumtaz diagnosed MDD in 34 participants by involving functional connectivity measured by EEG to the machine learning framework (Mumtaz et al., 2018).

Machine learning

Artificial Intelligence methods, or Machine Learning (ML), aim to predict with high accuracy new data based on patterns *learned* from previously collected data. Machine learning can be used to study patterns of brain activity in the EEG biomarkers that are specific for people with a decline in mood during winter. From that, the algorithm can be trained to predict mood decline based on EEG data that the algorithm has not *seen* during learning. How well a prediction model generalizes overall, i.e. how accurate it predicts previously unseen data, is measured by accuracy. Accuracy is the proportion of correctly classified samples (Jiang et al., 2017). In our case, sensitivity is the proportion of participants who will experience a sad mood in winter that were correctly identified. Specificity is the proportion of participants who will not experience a sad mood in winter that were correctly identified.

Cross validation

Patel, Khalaf and Aizenstein (2015) explained the cross validation procedure. The precision of a prediction model, the performance of new data in a model developed by ML, is evaluated by a validation procedure, usually

cross-validation. Different techniques can be chosen, k-fold cross-validation in the form of holdout of k samples, or leave-one-out-fold cross-validation, which is a special case of k-fold cross-validation with k=1. The data is divided into k sets of equal size, all sets except for one, which is the test set that is left out, form together the training set in one iteration.

1.2. Choice of research method

To our knowledge, seasonal mood fluctuations have never been predicted by a combination of EEG and psychological tests, and never by applying machine learning. Here follows an overview of methodological aspects of the current quantitative master's project, the research format, assessment methods and variables. Data collection, data analysis and participants selection - for example sampling method, sample size, and exclusion criteria - are described, and last not least ethics.

Research setting

The baseline assessment was performed between July and September 2019 in the EEG laboratory of the Faculty of Psychology at the University of Akureyri. Follow-up assessments were conducted in October, January and April 2020 via online questionnaires and telephonic reminders conducted by the research partners at University of Iceland. This study analysed only baseline data and follow-up in January. We were lucky to select data just before the sociopsychological effects of the corona pandemic appeared in January 2020.

Sample

Participants were recruited via email to the students at the University of Akureyri, as well as via advertisement in social media, directing interested individuals to a webform. Inclusion criteria were the minimum age of 18 years,

proficiency in Icelandic language, the presence in Akureyri to take the EEG measurements, access to an online computer, and the ability to give informed consent for participation. For completion of all follow-ups participants were remunerated with a voucher of 4,000 ISK for a shopping centre.

Data collection and analysis

The reason why we limited data collection to baseline and the follow-up in January was the question whether there was a vulnerability, capturable in summer. We had to discriminate between participants free of symptoms in summer, and those with seasonal mood fluctuations, and to exclude those, which suffered from depression all year round. The cut-off score for the severity label normal was less than 10 points at the emotional state of depression on the DASS21 (Lovibond & Lovibond, 1995). When participants had not answered all questions in the questionnaires, we excluded missing data.

Why EEG?

The combination of EEG with computer techniques in the last 25 years signifies an important, substantial advance in brain electrophysiology. The advantages of digital EEG are for example convenient selection for operating the recording system, and improving the interpretation of the EEG signals (Linvit Popa et al., 2020). The opportunity for non-invasive application, the easy way to collect data, the very high time resolution and being an inexpensive method to research neural activities let it be an attractive alternative over other brain research techniques (Freeman & Quiroga, 2012).

The EEG recording, pre-processing, feature extraction of the current study was performed with recording hardware and the package BrainVision Analyzer (version V001(09/2017) from Brain Products GmbH (Gilching, Germany). The

preprocessed data was analysed by Matlab (release 2018b, The Mathworks, Massachusetts, USA).

Why EEG at rest?

Studying neuronal activities by EEG allows us to investigate associated behavior under different conditions, for example at rest, absolving a baseline task with the eyes open or eyes closed (Amin et al., 2017; Rogala et al., 2020). We took EEG at rest to evaluate the intrinsic neural activities when participants were not activated by a task, e.g. in order to search for changes of alpha activities (Choi et al., 2019), the frequency range where most activity can be seen when people are wakefull or in a relaxed state (de Freitas et al., 2016). However, EEG-activity at rest may also reflect traits as they may be indicative for some intrinsic organization of brain networks. Therefore, connectivity measures at rest might be of interest.

Why EEG during cognitive tasks?

Neurophysiological studies of depression stated that cognitive and emotional tasks lead to cortical response, capturable by EEG, elucidating different levels of activities, and showing asymmetry of the brain hemispheres (de Freitas et al., 2016). Investigation of brain responses to certain stimuli might be more conclusive than EEG activity at rest as it might indeed be the response style to mood alterations that is predictive instead of some inherent trait

Why machine learning?

Compared to classical EEG studies with sample sizes of N=20, the current investigation created a relatively large data set. With high-dimensional features spaces like EEG measures of connectivity, selection of the most relevant biomarkers / features is required. Machine learning techniques have been developed to address this task, e.g. random forests, and lasso regularization.

Therefore, to answer the question of predictability, classification requires selection of meaningful features. Finally, those features and the models built on those features must be evaluated using cross-validation techniques (Fomina et al. 2015).

Why these questionnaires?

With the aim to test the prediction of cognitive vulnerabilities associated with symptom changes during winter, we measured symptoms as well as cognitive vulnerabilities. For symptoms of depression, anxiety, and stress we used DASS21, The Patient Health Questionnaire (PHQ9), The Perceived Stress Scale (PSS), and emotional reactivity by mood induction in the experimental task. We assessed rumination tendencies as a cognitive vulnerability by self report questionnaires about ruminative responses (The Ruminative Responses Scale, RRS), state rumination (The Brief State Rumination Inventory, BSRI, Marchetti et al., 2018), positive beliefs in rumination (The Positive Beliefs in Rumination Scale, PBRS), and habitual characteristics of negative thinking (The Habit Index of Negative Thinking, HINT, Verplanken et al., 2007).

The reason why questionnaires of habitual behaviors, for example the RRS and the HINT, are included as rumination measures in our data sampling is that RRS is the traditional measure of depressive rumination, and HINT was chosen because of its strong prediction. Hjartarson et al. (2020) has found that HINT scores predicted more persistent negative effects in a rumination induction task in the laboratory. In a study by Hjartarson et al. (2021) a stronger prediction of the temporal association between a negative effect at baseline and rumination after mood induction was observed. This result was observed via repeated sampling data through participants‘ smartphones in daily life, 10 times per day over six days. The BSRI as a 8-item brief questionnaire tests the state rumination, by measuring depressive ruminative thoughts of the participant.

Another self-report questionnaire of habitual routines and automatic tendencies is the Creature of Habit Scale (COHS), measuring repetitions of daily life activities (Ersche et al., 2017). Ólafsson et al. (2019) evaluated the psychometric properties of the questionnaires (for example HINT, COHS and RRS) in a study measuring the habitual behaviors among 225 Icelandic students. The researchers found psychometric properties of the Icelandic version of HINT and COHS to be *good*.

For the purpose of assessing seasonal fluctuations in mood and behavior, we used the 8-item SPAQ, containing the four topics: seasonality in mood, behavior, and pattern of seasonal change, response to various kinds of climate and atmosphere conditions, and the extend how much an individual will be affected by these changes (Murray, 2003). The psychometric properties of the Icelandic version of SPAQ, for example sensitivity (94%), specificity (73%) and positive predictive value (45%), measured in a study by Magnusson (1996), showed a relatively high value, and high validity of SPAQ to classify groups' likelihood to develop symptoms or not.

Why these biomarkers?

Biomarkers derived from the EEG can serve as a correlate of depression. In a study Höller et al. (2017) discussed the reliability of connectivity as a measure of neural activities. Biomarkers were tested regarding their reliability, concerning data length and discontinuity, frequency resolution and model construct. These multivariate parameters of feature extraction were: the *auto- and cross-spectrum*, the *direct causality,* the *transfer function,* the *transfer function polynomial*, the *real valued coherence*, the *complex coherence*, the *partial coherence*, the *partial directed coherence*, the *partial directed coherence factor*, the *generalized partial directed coherence*, the *directed transfer function*, the *direct directed transfer function*, the *full frequency directed*

transfer function, the *Geweke´s Granger causality*, and the *power spectral density.* The data analysis by these parameters was performed in a study, where baseline neuropsychological tests combined with EEG brain network measures were investigated in 40 patients with neurological diseases and 20 healthy controls. Reliability differed between model constructs and frequency ranges. Given available estimates of reliability, these biomarkers were selected for the present study. Moreover, another study demonstrated a sensitivity of 81% and a specificity of 90% to predict worsening of depressive symptoms (Höller et al., 2020). A multimodal assessment was chosen because psychological questionnaires and EEG of neural activity may complement each other, and can increase the prognostic accuracy of seasonal mood fluctuations.

Ethics

The Icelandic National Bioethics Committee confirmed the survey application on May 28th 2019 (study number 19-090-V1). All researchers and students who had direct contact to participants for gathering data signed a non-disclosure contract. All participants gave prior to inclusion written informed consent for participation, and were informed to have the right to stop participation whenever they wanted, without any indebtedness. All participants were offered psychological support if needed because of their participation. Participants were given numbers to protect anonymity, and the confidentiality of the participants´ personal data is ensured by storing the data at safe places in the responsibility of Dr. Yvonne Höller and Dr. Ragnar Pétur Ólafsson. Data will be destroyed after the work of the study ends.

Aim of the study and research question

Although SAD is rather rare, Iceland has the highest level of antidepressant consumption, because of a larger number of users and a longer time of

treatment. To lower the number of antidepressant prescriptions, a timely prevention of sad mood in winter would be warranted, depending on the early identification of people-at-risk to suffer from seasonal mood fluctuations already before the first symptoms occur in autumn. We want to determine whether cognitive vulnerabilities, or biomarkers of brain activity, or their combination is better suited to identify vulnerable individuals to seasonal mood fluctuations beginning in autumn, based on assessments conducted in summer.

Research Question:

Can we determine whether cognitive vulnerabilities, or biomarkers of brain activity, or their combination is better suited to predict seasonal mood fluctuations, based on assessments conducted in summer?

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2 Manuscript: a scientific journal article

Predictability of seasonal mood fluctuations based on electroencephalographic biomarkers, physiological and cognitive vulnerabilities in a non-clinical sample

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Abstract

Induced by decreasing light, people affected by seasonal mood fluctuations may suffer from low energy, have low interest in activities, experience changes in weight, insomnia, difficulties in concentration, depression, and suicidal thoughts. Few studies have been conducted in search for biological predictors of seasonal mood fluctuations in the brain, such as EEG oscillations.

A sample of 68 participants was examined with questionnaires and electroencephalography (EEG) in summer. In winter, a follow-up survey was recorded and participants were grouped into those with significant mood decline (N=20) and those without self-reported depressive symptoms both in summer and in winter (N=48). A support vector machine was trained to predict mood decline by either EEG biomarkers alone, questionnaire data at baseline

alone, or a combination of the two. Leave-one-out-fold cross validation and nested subset selection (lasso regularization) was used.

The accuracy for classification was at up to 76.12% for questionnaire data, 71.64% for EEG alone, and 82.09% for EEG combined with questionnaire data.

Questionnaire data was more conclusive than EEG biomarkers recorded in summer for prediction of sad mood in winter, but it is advantageous to combine EEG with cognitive stimulation as well as psychological assessment to boost predictive performance.

Keywords: seasonal mood fluctuations, EEG biomarkers, cognitive vulnerabilities, EEG biomarkers, prediction

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2.1 Introduction

Winter depression is the most common form of seasonal affective disorder (SAD), characterized by depressive symptoms in winter and remission in spring (Rosenthal et al., 1984; Magnusson and Partonen, 2005). As compared to major depressive disorder, patients with SAD exhibit atypical depression symptoms, especially hyperphagia and hypersomnia, but scoring lower in interpersonal sensitivity and rejection avoidance (Tam et al., 1997). The condition has been reported in many regions of the world, with 1-3% of adults being affected in temperate climates (Magnusson and Boivin, 2003), and being highly relevant in nordic countries with prevalence rates over 12% e.g. in Alaska, Denmark, Norway, and Siberia (Booker et al., 1991; Levine, 1995; Dam et al., 1998; Magnusson, 2000). The disorder was reported to be occurring over many years for most patients, with full remission within about 9 years being found in 14% of cases, only (Schwartz et al., 1996), although a later study suggests higher remission rates (Clery-Melin et al., 2018). Several reports criticise the defined borders between SAD, major depression, and the DSM criteria (Dittmann et al.,

1994; Thompson et al., 1995). However, SAD is usually not as severe as major depression but still has socioeconomic implications as it negatively impacts on quality of life and was suggested to increase the probability of unemployment (Tefft, 2012). Because of the relatively short period of SAD compared to the typical duration of psychotherapy and the long time it takes for serotonin-selective reuptake inhibitors to show an effect it might be wise to start prevention at least two months before onset of symptoms. In turn, this requires early identification of people at-risk to develop seasonal mood fluctuations. Therefore the search for characteristics and biomarkers with a high predictive value as well as a better understanding of vulnerabilities for SAD is highly warranted. If we could identify cognitive vulnerabilities for SAD, specific designs for psychotherapy could be developed. Both, the early estimation of the risk for seasonal mood fluctuations, and suggestions towards an effective psychotherapeutic intervention would be a tremendous improvement of mental health care.

Several attempts have been undertaken to predict sad mood in winter based on psychological examinations or biomarkers measured in summer. Biomarkers have mainly been derived from major biological hypotheses regarding circadian rhythms, neurotransmitters, and molecular genetics (Sohn and Lam, 2005). Circadian rhythms were suggested to be important in SAD, where according to the phase-delay hypothesis the patient's circadian rhythms are delayed relative to the daily routine of sleeping/resting and waking/activity (Magnusson and Boivin, 2003). SAD is especially common in younger subsamples and people with evening chronotype (Höller et al., 2021). Moreover, in patients with SAD, depressive symptoms are typically worse in the morning (Graw et al., 1991). These circadian aspects can be related to genotype, as a later sleep onset is related to melanopsin sequence variations, i.e. a specific genotype (Roecklein et al., 2012). Melanopsin gene variations explain variability in the post illumination

pupil response among individuals with SAD in such a way that individuals with SAD are less sensitive to light input (Roecklein et al., 2013).

The best indicator for a likely occurrence of depression in winter is the individual's report on prior experience of seasonal symptoms, e.g. according to the Seasonal Pattern Assessment Questionnaire (SPAQ, Murray et al., 2001). The SPAQ is still the most used instrument for estimating subjective experience of seasonal occurrence of depression symptoms. In patients with SAD, there is a bias towards remembering words of negative valence more likely in the winter than in the summer (Jensen et al., 2016). In addition to remembering negative words more likely, patients with depression also create more false memories than healthy controls and perceive even positive items with a less positive, i.e. more negative valence (Yeh and Hua, 2009). Individuals with SAD estimate future negative events as more likely to happen (Dalgleish et al., 2010), but this characteristic was never examined with respect to its predictive value in a longitudinal study. Individuals with SAD demonstrate a high level of automatic thoughts and dysfunctional assumptions (Hodges and Marks, 1998) as well as negative attributions (Levitan et al., 1998). Such psychological features, i.e. cognitive-behavioral factors such as increased rumination, automatic thoughts and dysfunctional attitudes were shown to be not only indicative (Rohan et al., 2011) but even predictive for SAD (Rohan et al., 2003). A ruminative response style as measured in fall predicts symptom severity in winter (Rohan et al., 2003) which indicates a predisposition for ruminative processes being mediators for SAD symptomatology. When examining rumination, it is crucial to distinguish between trait and state rumination (Marchetti et al., 2018), independent of the extent of trait rumination (Moberly and Watkins, 2008). Another study found that individuals with higher levels of dysfunctional attitudes, ruminative response style, and internal attributional style for negative events experienced more winterly sad mood and cognitive depression symptoms (Enggasser and Young, 2007). Emotional responses were also combined with

attention demands in an emotional Stroop task to predict subsequent levels of symptomatology with tests in winter and follow-up in summer (Spinks and Dalgleish, 2001). Although measurement in summer and follow-up in winter would be of greater interest for the identification of patients who might benefit from targeted prevention programs, this study revealed interesting insights into the relationship between lower emotional Stroop performance and more negative mood.

Another approach to identify vulnerability to seasonal mood changes and to find predictive biomarkers is based on neuroimaging. Since the brainstem is affected by photoperiodic changes, a large study used magnetic resonance imaging to determine a relation between brainstem volume and sad mood (Majrashi et al., 2020). In this study, a relationship between photoperiod, volume of whole brainstem, pons and medulla volumes, and sad mood and anhedonia was found only in women, but not in men. Related to the anomaly of cerebral serotonin transporter in female carriers of the short 5-HTTLPR genotype, a network including the ventral striatum, right orbitofrontal cortex, middle frontal gyrus, left supramarginal gyrus, left precentral gyrus, and left postcentral gyrus was found to be differentiating females with SAD from those without with respect to higher serotonin levels during winter (Nørgaard et al., 2017).

As neuroimaging and genetic testing is not widely available, the most convenient approach to predict seasonal mood fluctuations is a psychological examination. In order to boost accuracy of prediction a physiological marker could be added that is easily obtained at low cost, but commercial products for brain computer interfacing e.g. in the gaming industry raise the hope that soon there will be easy-to-use systems available that can combine the lightweight design of devices used in non-professional settings with the accuracy needed for clinical and research questions. In fact, it was found that EEG-biomarkers correlate with the absence of daylight and with midnight sun, as demonstrated by

a limited number of EEG studies in northern countries, and factors such as responsiveness of the brain to lighting conditions but also sleep was discussed to be the source of this variance (Soroko et al., 2013; Demin et al., 2014). The EEG is also indicative for depression and variants of it (de Freitas et al., 2016; Höller et al., 2017). The earlier mentioned valence effects of memorized visual stimuli are detectable in the early event-related components P1 and N1 in the EEG (Kuchinke et al., 2015), further suggesting top-down attentional modulation of emotional memory bias. Broadband lower absolute EEG-power was found in persons with MDD (Ding et al., 2019), but especially in the theta (Shim et al., 2017; Atchley et al., 2017) and alpha frequency band and especially in the frontal cortex (Cisler and Koster, 2010; Ding et al., 2019; Gollan et al., 2014; Kaiser et al., 2018; Park et al., 2019). The prefrontal cortex is also involved in rumination (Ferdek et al., 2016; Putnam and McSweeney, 2008; Rosenbaum et al., 2018). Most importantly, beta and alpha power varies with seasons (Barbato et al., 2018; Machleidt and Gutjahr, 1984), and so does frontal alpha asymmetry (Velo et al., 2012). Abnormalities in beta and alpha power as well as frontal alpha asymmetry are also specific for SAD (Allen et al., 1993; Passynkova and Volf, 2001; Teicher et al., 1996; Volf et al., 1993; Volf and Passynkova, 2002). In the current study we aim to identify biomarkers in the EEG, self-reported characteristics, and cognitive vulnerabilities which, when measured in summer, allow prediction of sad mood in winter.

2.2 Methods

Ethics

We obtained prior approval from the Icelandic National Bioethics Committee on May 28th 2019 (study number 19-090-V1). All investigators signed a non-disclosure contract and all participants gave their informed consent.

Research setting

The study was carried out as a collaboration between the University of Akureyri and the University of Iceland. The baseline assessment was performed between July and September 2019 in the EEG laboratory of the Faculty of Psychology at the University of Akureyri. Follow-up assessments were conducted in October, January, and April 2020 via online questionnaires and telephonic reminders conducted by a team at the University of Iceland. For the purpose of the present manuscript, only data from the baseline and follow-up in January 2020 was analyzed.

Recruitment

Participants were recruited via email to students at the University of Akureyri, as well as via advertisement in social media, directing interested individuals to a webform. Inclusion criteria that the participants were 18 years or older, understanding Icelandic, and able to give informed consent for participation. For completion of all follow-ups participants were remunerated with a voucher of 4,000 ISK for a local shop.

Procedure

Baseline assessment took about 120min. After participants completed informed consent, a digital questionnaire, consisting of 72 custom made questions and the questionnaires as listed in section 2.5 were answered by the participants. While participants answered the questions, the EEG was mounted. Electrodes were filled with electrolyte containing a mild abrasive and skin was degreased when necessary in order to achieve impedances below 10 Ohm. When satisfactory impedance was achieved and participants had completed all questionnaires the lights were dimmed, the doors closed and the laboratory made ready for recording. Before recordings began participants were shown the effect of muscle movement on the EEG and consequently instructed to keep movements to a minimum and asked to refrain from talking during the recordings.

The first two conditions were resting state measurements which lasted for 3 minutes, with eyes open and eyes closed respectively, and with the screen of the stimulus computer turned off. The other tasks were presented on a stimulation computer with experimental code implemented in Matlab (version 2018b), based on the Psychtoolbox. The first condition was memorizing pictures from the OASIS database (Kurdi et al., 2017) on the stimulus computer, balanced for negative, neutral and positive valence and low, medium, and high arousal. Participants were informed that in the subsequent task they would be asked to recall the pictures shown. The task required to indicate whether each picture represented spring, summer, fall or winter by pressing a corresponding key on the keyboard with the right hand. Pictures were shown with an inter-trial interval of 1 sec and a variance of 0-10 screen flip intervals during which a fixation cross was presented. All pictures were shown for at least 2 sec and otherwise until participants responded via key press. This procedure should ensure attention and prime seasonal effects on memory. For the next condition, the picture recall task, the screen of the stimulus computer was once again turned off and the participants were asked to freely and verbally recall which pictures they remembered seeing in the previous task. Their answers were noted by the experimenter. Subsequently a recognition condition involved presentation of the pictures from the picture learning task but randomly intermixed with 60 new images, again balanced for valence and arousal. Participants were asked to indicate with a corresponding key on a keyboard whether each picture was new or previously seen. Timing of the presentation was the same as in the learning condition. The next condition was a Stroop task where participants were asked to indicate the font colour of words displayed on the stimulus computer by pressing a correspondingly coloured key on a keyboard. There were 105 congruent trials and 210 incongruent trials, presented in a randomized order, with an inter-trial interval of 1 sec and a variance of 0-10 screen flip intervals during which a central fixation cross was presented.

In the final condition, the rumination task, participants received a printed three part form containing questions about their current emotional state and the Brief State of Rumination Inventory (BSRI, Marchetti et al., 2018). All instructions were given verbally through headphones or on screen in the stimulus computer. Firstly, participants completed part A on the form containing one question on their current emotional state and the 8-item BSRI. Next, an 8 minute musical piece was played in order to evoke temporary sadness or dysphoria, and participants asked to freely experience any emotions they might feel. We used a musical excerpt from Prokofiev's *Russia Under the Mongolian Yoke*, remastered at half speed. Prior research has shown that this approach can effectively cause a transient dysphoric mood (Jarrett et al., 2012; Lau et al., 2004; Martin, 1990; Ólafsson et al., 2020).

Immediately after the song had finished, participants answered the forms' part B containing one question on their current emotional state. They were then instructed to wait in silence for 5 minutes for a challenging cognitive task. However, no cognitive task followed but the waiting period served as a free contemplation time in anticipation of a task. In the third and final part of the rumination task participants answered an 8-item BRSI and one question on their current emotional state.

On the day following the EEG recording, participants began the baseline measurement of the studies follow-up phase which consisted of a four day long measurement period using the mobile application ExperienceSampler (Thai and Page-Gould, 2017) with which mood fluctuations over the course of a day along with activity level, fatigue and rumination was assessed in questionnaire form. Five measurements were taken at random times each day between 9:00 and 21:00.

The three subsequent follow-up intervals, conducted in October, January and April, were in the same form as the baseline measurement with the addition

of a 48 question internet survey. The internet survey consisted of the following questionnaires: Patients Health Questionnaire, Rumination Responses Scale-short form, Perceived Stress Scale, and Depression Anxiety Stress Scales (see section 2.5 for more details). In addition, the survey included questions on recent traveling and use of any depression treatments.

Questionnaires

We assessed subjective perception of mood and behavioural change with seasons with the Seasonal Pattern Assessment Questionnaire (SPAQ, Rosenthal et al., 1984). It includes 8-items regarding seasonal change in mood and behaviour, pattern of seasonal change, reactivity to different climatic and atmospheric conditions and whether and to what extent those changes affect the individual (Murray, 2003). We used the Icelandic version, which performed compared to a diagnostic clinical interview with a sensitivity of 94%, a specificity of 73% and a combined positive predictive value of 45% for SAD and subsyndromal SAD (Magnusson, 1996). The questionnaire is acknowledged as an effective screening tool for SAD, with an internal consistency of alpha=0.74 to 0.81 and a test-retest reliability of 0.76 at an interval of 2 months.

As mentioned in section 2.4, we examined state rumination before and after mood induction with the 8-item BSRI (Marchetti et al., 2018). The Ruminative Responses Scale-short form (RRS, Treynor et al., 2003) was used to measure the degree of trait rumination.

The Habit Index of Negative Thinking (HINT, Verplanken et al., 2007) measures in 12 items habitual characteristics of negative thoughts (i.e. automaticity, lack of intent and awareness, difficult to control). In addition, we measured mood with the Patient Health Questionnaire (PHQ, Kroenke et al., 2001), sleep problems with the Bergen Insomnia Scale (BIS, Pallesen et al., 2008), depression, anxiety and stress with the Depression Anxiety Stress Scale (DASS, Lovibond and Lovibond, 1995), positive attitudes towards ruminative

thinking with the Positive Beliefs in Rumination Scale (PBRS, Watkins and Moulds, 2005), optimism with the Life Orientation Test Revised (LOT, Scheier et al., 1994), subjectively rated current stress with the Perceived Stress Scale (PSS, Cohen and Williamson, 1988), chronotype by using the Morningness Eveningness Questionnaire - Revised (MEQ-R, Horne and Ostberg, 1976), and to what extent people were following habits with the Creature of Habit Scale (COHS, Ersche et al., 2017). Participants were also asked about their age, gender, handedness, first language, body weight and height from which we calculated the Body Mass Index (BMI).

Furthermore, we asked about nutrition, mental and neurological diseases, regularly taken medication, current tiredness, bed and wake time the night before the experiment, exercise, phase of menstrual cycle in women, and weather, but we did not include the respective data into the current manuscript.

EEG recording and preprocessing

EEG data was recorded with software and hardware from Brain Products GmbH (version V001(09/2017, Gilching, Germany) at a sampling rate of 1,000 Hz with an EasyCap in an extended 10-20 system, including 32 electrodes (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T7, T8, P7, P8, Fz, Cz, Pz, FC1, FC2, CP1, CP2, FC5, FC6, CP5, CP6, FT9, FT10, TP9, TP10) referenced to FCz and grounded at AFz. In addition, lower vertical electrooculograma was recorded.

EEG-data was pre-processed with BrainVision Analyzer (Brain Products GmbH, Gilching, Germany). First, band-pass filters from 0.5-48 Hz with zero-phase shift Butterworth filters were applied. Then, data was referenced to the common average. Next, an independent component analysis (ICA) was used such that in the back transform the signals that include eyeblink artefacts would be removed (infomax restricted algorithm). Finally, remaining artefacts were identified and excluded automatically by the following standard thresholds:

check gradient (maximal allowed voltage step: 50 microvolt/ms), check difference (maximal allowed difference of values in intervals of 200ms: 200 microvolt), lowest activity allowed in 100ms intervals: 0.5 microvolts. The artefacts that were identified in this way were excluded with a time-range of +-200ms.

The EEG at rest was recorded with eyes open and with eyes closed, 3 minutes each, then the whole recall session, and the last 3 minutes out of 5 minutes of sad mood induction was segmented into equal-sized epochs of 2 seconds. From the learning and recall conditions 1 second starting at stimulus presentation were extracted, and they were processed separately for negative, neutral and positive pictures for learning, and in addition for old and new pictures for recognition. From the Stroop task 500ms from stimulus onset, and congruent and incongruent conditions were processed separately. Thus, in total, there were 15 conditions extracted from the EEG experiment that were submitted to feature extraction.

Feature extraction

For all of these conditions and each segment we extracted features based on the multivariate autoregressive model (MVA) with the functions *mvfreqz.m* and *mvar.m* from the BioSig toolbox (Schlögl and Brunner, 2008) with model order 10, and partial correlation estimation with unbiased covariance estimates (Marple, 1987), which is an accurate estimation method (Schlögl, 2006). The multivariate parameters in the frequency domain that can be derived from these transfer functions were computed for 1 Hz frequency steps between 1 and 48 Hz. The measures that were extracted were the following:

- **Spectrum:** The auto- and the cross-spectrum, which is the Fourier transform of the cross-covariance function (Murthy, 1963)
- **Direct causality:** Direct causality as developed by Kaminski et al.(2001); this measure is not computed for each frequency.

• **Transfer function**: Related to the non-normalised directed transfer function (Eichler, 2006).

• **Transfer function polynomial:** Frequency transform of a polynomial describing the transfer function. It is related to coherence as the absolute of the squared transfer function polynomial represents the non-normalised partial directed coherence (Eichler, 2006).

• **Real valued coherence:** The real part of the complex-valued coherence (Nolte et al., 2004) is an ordinary coherence (Schlögl and Brunner, 2008).

• **Complex coherence:** The imaginary part of the complex-valued coherence (Nolte et al., 2004).

• **Partial coherence:** Designed by Gersch and Goddard (1970) it's concept is that one channel drives the other channels if the first channel explains or accounts for the linear relation between the other two.

• **Partial directed coherence**: An extended concept of partialised coherence, measuring the relative strength of the direct interaction between pairs of signals (Baccalá and Sameshima, 2001).

• **Partial directed coherence factor:** An intermediate step between partial coherence and partial directed coherence by adding directionality to partial coherence and including instantaneous causality (Baccalá and Sameshima, 2001).

• **Generalized partial directed coherence:** In contrast to partial directed coherence, generalized partial directed coherence is invariant against scaling differences between signals (Baccalá et al., 2007; Taxidis et al., 2010).

• **Directed transfer function:** represents information that flows from one region to another over many possible alternative pathways (Kaminskí and Blinowska, 1991).

• **Direct directed transfer function:** extends directed transfer function by separating direct from indirect causal relations of signals (Korzeniewska et al., 2003).

• **Full frequency directed transfer function:** In contrast to directed transfer function, the full frequency directed transfer function is normalised with respect to all the frequencies in the predefined frequency interval (Korzeniewska et al., 2003).

• **Geweke's Granger Causality:** A bivariate version (Bressler et al., 2007) of Geweke's Granger Causality (Geweke, 1982).

Finally, we also included the power-spectral density as a feature, representing band-pass power in 1Hz frequency steps from 1Hz to 48Hz.

Features and feature combinations for machine learning

For classification, we considered three situations:

• EEG features only; each EEG feature was used individually, i.e. we conducted for each of the 15 conditions classification with each of the 16 feature vectors as described in section 2.7.

• Questionnaire data only; We classified participants by a feature vector including their total scores in PBRS, COHS, the three mood measurements in the mood induction task and the two rumination measurements with the BSRI in the mood induction task, SPAQ global seasonality score, HINT, PHQ, DASS stress, anxiety, and depression, PSS, RSS brooding and reflection, sex, age, education, BMI calculated by the participants' indication of height and weight, MEQ, BIS, and LOT.

• A combination of each of the EEG features and conditions with the questionnaire feature vector.

Machine learning and statistical analysis

For machine learning we divided the sample into those participants who would increase their depression scores on the DASS-21 with at least 10 points, i.e. the group experiencing winter depression, as compared to a control group which would not be depressed at baseline as well as in winter, i.e. showing less than 10 points on the DASS-21 depression scale at both timepoints. The minimum increase of 10 points was chosen as the normal range of scores for the DASS-21 is 0-9 points (Lovibond and Lovibond, 1995). Moreover, reporting a depression level at baseline and at follow-up led to participant exclusion, that means, if their depression score at baseline and in January 2020 was at least 10 according to the DASS-21. We used leave-one-out cross-validation, thus, a model was fitted for each participant to all participants but the left-out participant using the Matlab (2018b) function *fit-linear* using a logistic regression as learner. The fitting procedure was repeated for a regularization term strength λ of 10^{-11}.We used lasso (L1) penalty for the composition of the objective function for minimization from the sum of the average loss function, with sparse reconstruction by Separable Approximation (SpaRSA) as objective function minimization technique and 10^{-8} as gradient tolerance. The initial linear coefficient estimates were set to zeros as initial values and the learning rate was constant.

Lasso regularization reduces the number of predictors, identifies important predictors and selects among redundant predictors, which is important in the high-dimensional feature space of EEG biomarkers extracted with the multivariate autoregressive model. As λ increases, the number of nonzero components of β increases. Intuitively, the predictor coefficients β are therefore indicative for each feature's importance to the model and were therefore reported

with the results to demonstrate which brain regions/frequency range contributed most to the prediction of development of sad mood in winter.

2.3 Results

Sample

From 119 participants in the baseline assessment, 89 participated in the second follow-up in winter (January 2020). After exclusion of missing data (because participants skipped questions in the questionnaire), 20 participants showed significant worsening of depression from baseline to follow-up, 48 entered the control group.

In the control group, age ranged from 19-66 years with the average age of 33.49 (median=28; SD=18.03). The control group sample consisted of 91% women. In the so-called *SAD group*, age ranged from 18-64 years with the average age of 28.95 (median=27.5; SD=17.38) years. The control group sample consisted of 14 women and 6 men. The two groups did not differ significantly by age (z=0.75; p=0.45). The odds ratio for gender to suffer from SAD is 1.8 according to Magnusson and Stefansson (1993) justifying an overall overrepresentation of female participants.

In the sample of controls/*SAD*, 8.51/15% had completed primary education, 48.94/45% had higher education entrance qualification, 2.13/10% had learned a trade, 27.66/15% had completed undergraduate education at an university, and 10.64/5% had completed master or doctoral level education at an university.

Descriptive statistics for the psychometric scales, separately for the two groups as well as results from Mann-Whitney U-tests comparing the two samples are shown in Table 1.

Classification results

For questionnaire data only, accuracy was 0.73, with a specificity (accuracy to classify control group participants correctly) of 0.70 and sensitivity (accuracy

to participants who would experience sad mood in winter) by 0.80. Figure 1 shows the predictor coefficients β for each feature's importance to the model for

Table 1: Psychometric characteristics of the control group and *SAD* group at baseline.

	controls		*SAD*		U-Test	
scale	mean	SD	mean	SD	z	p
BIS	11.7	7.44	17.45	8.98	-2.48	0.01
BMI	25.98	6.75	25.22	10.99	-0.22	0.83
BSRI t1	214.85	155.69	316.9	182.87	-2.09	0.04
BSRI t2	223.7	192.74	310.76	219.39	-1.54	0.12
COHS	78.68	21.08	80	36.64	-1.65	0.10
DASS anxiety	2.81	4.2	8.1	6.54	-3.55	<0.01
DASS depress	2.81	2.72	5.9	5.64	-2.02	0.04
DASS stress	8.21	6.38	14.9	9.3	-2.83	<0.001
GSS	5.53	4.7	9.95	4.97	-3.23	<0.001
HINT	29.6	17.04	54.1	17.87	-4.46	<0.001
LOT	7.45	3.86	3.45	4.62	2.97	<0.001
MEQ	15.38	3.81	13.3	5.23	1.67	0.09
mood t1	107.61	37.57	102.67	23.8	1.52	0.13
mood t2	75.6	39.81	73.04	37.77	0.27	0.78
mood t3	93.06	37.49	87.01	31.83	0.97	0.33
PBRS	23	6.24	23.7	3.91	-0.51	0.61
PHQ	4.09	3.06	8.2	4.18	-3.71	<0.001
PSS	7.09	2.4	8.15	1.81	-1.72	0.09
RRS b	8	2.6	10.25	3.85	-2.72	0.01
RRS r	8.15	3.09	9.95	3.19	-2.12	0.03

BIS: Bergen Insomnia Scale; BMI: body mass index BSRI: Brief State Rumination Inventory; t1: before mood induction; t2: after sad music; t3: after mood induction; COHS: Creature of Habit Scale; DASS: Depression, Anxiety, Stress Scales; GSS: Global Seasonality Score; HINT: Habit Index for Negative Thinking; LOT: Life Orientation Test; MEQ: Morningness-Eveningness Questionnaire; mood: emotional state;; PBRS: Positive Believes in Rumination Scale; PHQ: Patient Health Questionnaire; PSS: Perceived Stress Scale; RRS b: Ruminative Response Scale, brooding; RRS r: RRS, reflection

the prediction of development of seasonal mood changes. Predictive for experiencing sad mood in winter were large scores of insomnia according to the BIS, depression (both for the DASS and PHQ), anxiety, and stress, and habits of negative thinking. BMI, optimism, morningness, positive beliefs in rumination achieved highly negative predictor coefficients.

When using EEG data, this resulted in 15 times 16 classifications for each condition and each feature used. EEG alone yielded best classification accuracy for *direct directed transfer function* extracted during recognition task, specifically perception of pictures that are new and depicting negative content (accuracy: 71.64%, specificity: 77.08%, sensitivity: 57.89%).

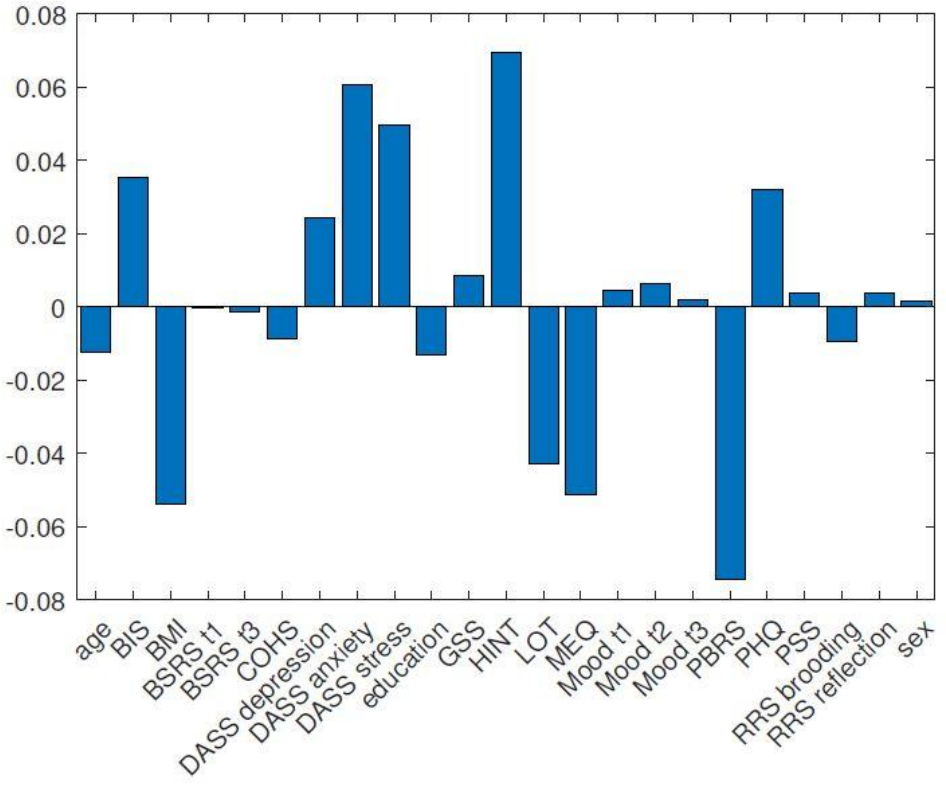

Figure 1: Predictor coefficients β for each questionnaires' importance to the model for the prediction of development of seasonal mood fluctuations.

Predictor coefficients β for this feature are given in figure 2, showing which brain connections were most predictive. In the delta range, fronto-occipital, fronto-central, and centro-central connections were most predictive, while in the theta, alpha and beta range only fronto-frontal and centrocentral connections seemed to play a role. There seems to be a lateralization to the right hemisphere, especially with respect to the central region in the theta, alpha and beta frequency range.

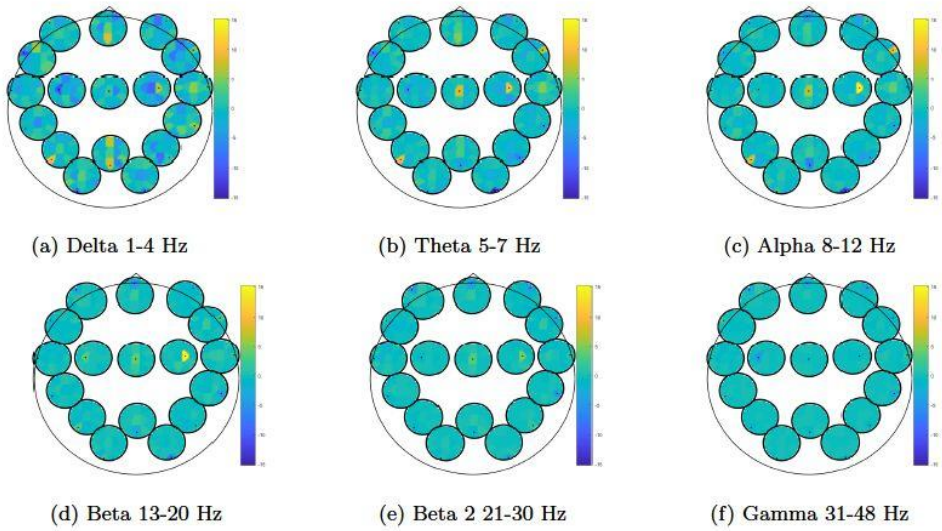

Figure 2: Predictor coefficients β for direct directed transfer function (dDTF) extracted during recognition task, specifically perception of pictures that are new and of negative valence. Coefficients indicate importance of the feature to the model for the prediction of development of seasonal mood fluctuations.

EEG combined with questionnaire data yielded best classification accuracy for *spectrum* with an accuracy of 82.09% extracted during rest with eyes open (specificity: 80.85%, sensitivity: 85%) and for *power spectral density* extracted during the recognition task, specifically perception of pictures that are old and depicting neutral content as well as pictures that are old and depicting neutral content (both with the same values: specificity: 82.98%, sensitivity: 80%). Predictor coefficients β for this feature are given in figure 3 and figure 4,

showing where in the brain oscillatory activity in a certain frequency band was most predictive for EEG during recognition of positive and neutral pictures, respectively. However, the pattern of predictor coefficient distribution across frequencies and brain lobes looks quite similar across the two conditions. In delta, mostly negative coefficients indicate involvement of occipital and right frontotemporal regions. Positive predictor coefficients were found right parietal and left frontally in delta, theta, alpha and lower beta range.

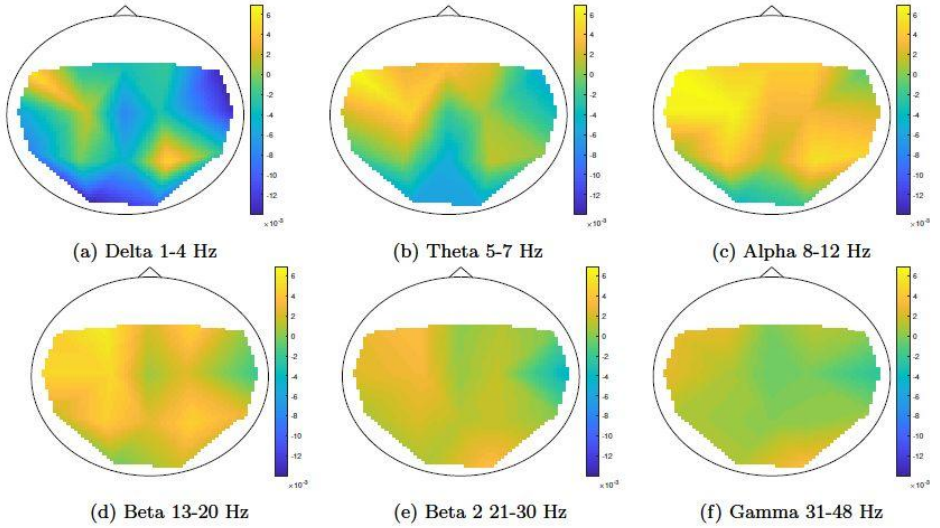

Figure 3: Predictor coefficients β for questionnaire data combined with power spectral density extracted during recognition of pictures that are old with positive valence. Coefficients indicate importance of the feature to the model for the prediction of development of seasonal mood fluctuations.

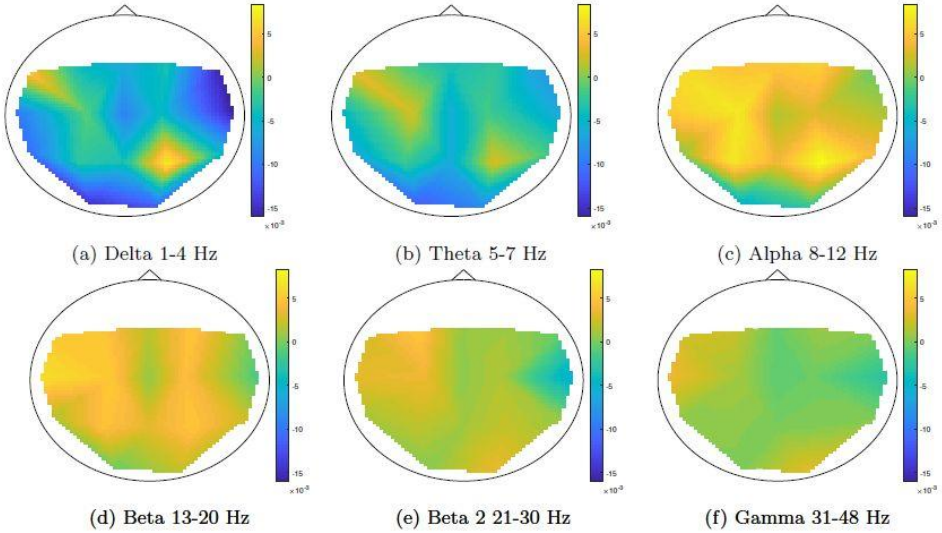

Figure 4: Predictor coefficients β for questionnaire data combined with Spectrum extracted during recognition task, specifically perception of pictures that are old and of neutral valence. Coefficients indicate importance of the feature to the model for the prediction of development of seasonal mood fluctuations.

2.4 Discussion

To identify biomarkers in the EEG, self-report questionnaires, and cognitive vulnerabilities which, when measured in summer, can be used for accurate prediction of whether an individual will suffer from a sad mood in winter, was our aim. We found that indeed, a combination of cognitive aspects and EEG biomarkers allow for a better prediction than the cognitive aspects or EEG biomarkers alone. In the following, we discuss these aspects as well as limitations of our study.

Self-report questionnaires and cognitive vulnerabilities

According to the cognitive vulnerabilities that showed larger predictor coefficients we found that insomnia, depression, anxiety, stress, and habits of negative thinking, as well as a low BMI, low optimism, eveningness, and low scores on the positive beliefs in rumination scale predicted sad mood in winter.

Insomnia or, more generally, sleep problems were related to SAD in earlier studies (Albert et al., 1991; Anderson et al., 1994; Booker et al., 1991; Borisenko et al., 2015; Höller et al., 2021; Johnsen et al., 2012; Koorengevel et al., 2002; Tonetti et al., 2014; Sandman et al., 2016). However, insomnia might not be a cognitive vulnerability, but rather a symptom of a physiological vulnerability. It has been suggested that in some cases, insomnia could be treated by administration of melatonin (Low et al., 2020), and there have also been attempts to treat SAD by melatonin (Danilenko and Putilov, 2005; Nussbaumer-Streit et al., 2019). Further evidence links melatonin to the serotonergic system, which in turn, is linked to depression, anxiety, and stress (Graeff et al., 1996). Melatonin treatment alters the expression of genes of serotonergic neurotransmission in a mouse model of SAD (Nagy et al., 2015). More evidence points to involvement of major monoamine neurotransmitters serotonin, norepinephrine, and dopamine in SAD (Levitan, 2007). Therefore, biochemical markers such as cortisol awakening response as a marker for hypothalamic-pituitary-adrenal axis function (Agustini et al., 2019) and serotonin-transporter binding (Mc Mahon et al., 2016) have been suggested. Being a serotonin-transporter-linked polymorphic region (5-HTTLPR) short allele carrier was found to be a risk factor for developing SAD (Rosenthal et al., 1984). A genotype-dependent increase in winter of serotonin transporter binding was found to be specific for patients with winter depression (Mc Mahon et al., 2016). However, although the level of serotonin transporter binding is comparable between healthy controls and depressed patients with winter during summer; the patient group showed a lower increase from summer to winter as compared to controls (Mc Mahon et al., 2016). The link to the serotonergic system is supported by predictability of relapse during winter based on depressive symptoms during tryptophan depletion in summer (Neumeister et al., 1999). Possibly related to neurotransmitter systems, low vitamin D3 levels were

also suggested to predict depressive symptoms increase from fall to winter (Kerr et al., 2015).

Habits of negative thinking were assessed with the HINT, where negative thoughts are characterized by automaticity, lack of intent and awareness, and difficulty to control them (Verplanken et al., 2007). Individuals with SAD also expect negative experiences in the future (Dalgleish et al., 2010), which is a concept closely related to the habit of negative thinking as well as the optimism-pessimism as assessed in our study. Endorsement of emotional adjectives and a negative attributional style are elevated in patients with SAD (Dalgleish et al., 2004). However, in contrast to our data it was previously reported that these cognitive aspects could not be used to predict later symptom levels (Dalgleish et al., 2004). Also, countering our expectations, a lower score in summer on the PBRS indicated a higher risk for sad mood in winter. Prior research showed that rumination is linked to depression (Takano et al., 2019) and that positive beliefs about rumination are associated with ruminative thinking, mediating further a negative association with positive affect (Kubiak et al., 2014). While prior research suggests that increased rumination is predictive for SAD (Rohan et al., 2003), we could not confirm this relationship. In our data, a negative predictor coefficient for the PBRS suggested that positive beliefs in rumination would rather prevent development of seasonal mood changes. This finding is difficult to explain but warrants further investigation. The first 4 items of the Icelandic translation (e.g. *I need to consider things to realize how I feel.*) of the scale could have been rather interpreted as being indicative for a positive attitude towards being considerate, which might indeed be a protective factor instead of a risk factor.

Furthermore, patients with prior experience of seasonal mood fluctuations respond depressively to a low light exposure in an experiment (Rohan et al., 2003), another indicator for emotional responses to darkness. However, as this result is based on prior experience of SAD, it might rather be due to reactivated

memories of sad mood during the dark period rather than an indicator for emotional response style. In line with the potential role of memory mechanisms, autobiographical memory style was examined in winter in individuals with SAD (Dalgleish et al., 2001). It was found that the number of overly general memories that were generated in response to positive cues was related to symptom levels measured during remission in summer (Dalgleish et al., 2001).

Finally, even more than being true for insomnia, our finding that a low BMI in summer can serve as a predictor for development of sad mood symptoms in winter could be seen as a physiological rather than a psychological symptom. The relation between body weight and SAD has also been investigated previously. A higher BMI at baseline was found to predict treatment outcome of 6 weeks light treatment (Dimitrova et al., 2017). As emotional eating and weight gain are associated with SAD (Kräuchi et al., 1997), our finding seems to be unexpected. However, it was shown recently that the self reported seasonal changes in weight are related to lower plasma adiponectin levels, an indicator for metabolic dysregulation (Akram et al., 2020). Therefore, it might be that the difference in weight between summer and winter is more relevant, and a lower BMI in summer might be indicative for a larger weight gain. This is pure speculation and needs to be addressed in future studies.

EEG biomarkers

Best EEG-related results were obtained during recognition of emotional pictures, which indicates that memory systems activation might be beneficial when gathering biomarkers from brain activity. It was reported previously that adjective memory in healthy patients and those affected by SAD showed no difference (Dalgleish et al., 2004) but that autobiographical memory style is related to symptom levels at remission in summer (Dalgleish et al., 2001). These partly contradicting findings suggest that further investigation of memory and memory related brain activity in SAD is highly warranted.

Our findings point to the involvement of a broad frequency range from delta to beta, and specifically frontal and central regions. EEG studies have identified some likely structural and activational irregularities being candidates for the neurological mechanisms involved in depressive tendencies and depressive mechanisms such as rumination. For example, lowered alpha activity in the prefrontal cortex is thought to predict higher tendency to ruminate (Putnam and McSweeney, 2008). Inefficient information transfer from the left dorsolateral prefrontal cortex to the temporal lobe structures might be critical for trait rumination (Ferdek et al., 2016). The involvement of the frontal cortex as well as the alpha frequency range points to the role of cognitive control over negative thoughts. High alpha power is acknowledged to reflect active inhibition (Klimesch, 1999). Therefore, the involvement of alpha activity in the left hemisphere can be interpreted as reduced cortical activity. It was theorized that hypoactivation of the left frontal area leads to ruminative tendencies and consequently to negative emotional interpretation (Disner et al., 2011). The frontal cortex is also involved in cognitive flexibility (Kim et al., 2011), which has been reported to be impaired in individuals with depression (Murphy et al., 2012). Specifically, individuals with major depressive disorders were suggested to exhibit ruminative and automatic thoughts within a negative schema because being cognitively inflexible in a negative emotional context (Deveney and Deldin, 2006).

An abnormal activation in the lower left frontal cortex has been found to be critical regarding depressed individuals' tendency to pay greater attention to adverse stimuli (Cisler and Koster, 2010; Ding et al., 2019). Abnormalities in the activation or structure of the circuitry of emotion, which includes the prefrontal cortex, anterior cingulate cortex, hippocampus and amygdala have been suggested to underlie depressive disorders (Davidson et al., 2002). In addition to the alpha abnormalities, abnormal synchronization of theta and beta oscillations was suggested to reflect unstable states of cognitive processing, specifically of

working memory in individuals with depression (Li et al., 2017). Analysing EEG band power beyond the alpha frequency range provided evidence which suggests that decreased theta power might be important during rumination (Shim et al., 2017), and lower power in the theta range, as well as alpha frequency band has been noted during mind wandering (Atchley et al., 2017). Moreover, increases in the delta band are generally related to pathology such as mental slowing in dementia (Cassani et al., 2018), as well as psychopathology (Newson and Thiagarajan, 2019).

Limitations

It was recently shown that the application of artificial intelligence to research depression by neuroimaging led to overestimating the classification accuracy in small sample sizes (Flint et al., 2021). This is a well known phenomenon when the number of features describing the samples exceeds the size of the sample and is not limited to neuroimaging but any modality where the feature vector is long. Certainly, our sample size is very small, as well. Therefore, we have chosen lasso regularization as an approach to address those problems of high-dimensional feature spaces.

It was found that there are significant effects of weather in some individuals with SAD, affecting energy (Albert et al., 1991). We did document current weather conditions at baseline, but not at follow up, which would have been needed in order to control effectively for interaction of seasonal symptoms with weather.

We also need to re-emphasize that this study included the GSS score as a measure for seasonality and other self-assessment questionnaires to measure depressive symptoms, while a clinical interview was not part of the study to ascertain diagnosis of SAD. Therefore, we limit our conclusions to results from a non-clinical sample.

Future directions

The use of psychological characteristics to predict seasonal affective occurrence can be extended to prediction of treatment response. Negative attributional style predicted poor response to pharmacotherapy in nonseasonal depression but not in seasonal affective disorder (Levitan et al., 1998). It was also reported that psychic anxiety was related to response to light therapy while somatic anxiety was rather related to a negative outcome (MacKenzie and Levitan, 2005), and that atypical symptoms of depression predict responsiveness to light therapy (Nagayama et al., 1991). There have also been attempts to predict treatment outcome in order to determine which patients might respond to light therapy (Terman et al., 1996), or which patients respond better to light therapy than CBT (Camuso and Rohan, 2020), or a combination of the two (Sitnikov et al., 2013). When patients exhibit cognitive vulnerabilities, the use of CBT might be crucial (Sitnikov et al., 2013). In a later study cognitive vulnerability could not be replicated as a prognostic or prescriptive predictor of outcome of light therapy vs. CBT, but morning types experienced less depression episodes after both kinds of therapy (Camuso and Rohan, 2020). It is possible that EEG-biomarkers could add to the planning of personalized treatment of patients with seasonal mood fluctuations, both by helping to select the most appropriate therapy alongside with the consideration of cognitive vulnerabilities, as well as by identifying individuals at risk in order to initiate preventative treatment in a timely manner.

2.5 Conclusions

Sad mood in winter may be predicted by questionnaire data, specifically psychological questionnaires, or EEG measures collected in summer, alone, but the combination of features from both domains is advantageous and leads to higher prediction accuracy. Our findings on relevant EEG biomarkers emphasize

the importance of frontal brain regions in the vulnerability for seasonal mood fluctuations as well as a broad frequency range.

2.6 Author contributions

Conceptualization, Y.H. and R.P.O.; methodology, Y.H. (for EEG), and R.P.O. (for psychological tests); software, Y.H.; validation, Y.H.; formal analysis, Y.H.; investigation, Y.H.; data curation, Y.H.; writing, original draft preparation, Y.H., G.K.K. and M.M.U.; writing, review and editing, Y.H., G.K.K. and M.M.U.; visualization, Y.H.; supervision, Y.H. and G.K.K.; project administration, Y.H.; funding acquisition, Y.H. All authors have read and agreed to the published version of the manuscript.

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2.9 Conflicts of interest

Declaration of interest: none.

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