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PhD Thesis

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"I should have been a bear. Bears are allowed to hibernate; humans are not"

– A Study of Cognitive and Personality Factors Involved in Seasonal Affective Disorder

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Title: "I should have been a bear. Bears are allowed to hibernate; humans are not" – A study of cognitive and personality factors involved in Seasonal Affective Disorder

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THESIS SUMMARY

People living in countries far north or south of Equator are subjected to cold, dark and long winters. Although most people cope well with the winter season, about 12% of the population in Copenhagen fulfil the diagnostic criteria for Seasonal Affective Disorder (SAD); an occurrence of recurrent seasonal depressions that most often develop during autumn or winter and remits the following spring or summer. Individuals with depression often exhibit cognitive impairments, but it is unclear which aspects of cognition are affected in SAD, whether they are state or trait features of depression, and are implicated in the development of depressive symptoms. Similarly, the impact of personality traits on SAD severity, and whether such self-reported traits fluctuate with the seasons is also unknown.

The overall aim of this thesis is to gain more knowledge on how cognitive functions and self-perceived personality traits are involved in SAD, and how they associate with depressive symptoms. This thesis is based on three published studies that have been undertaken in a group of 29 medication-free individuals diagnosed with SAD and 30 demographically matched healthy controls. All participants completed an extensive neuropsychological test battery, self-report questionnaires and psychiatric interviews once in summer and once in winter.

We observed that in winter, individuals with SAD showed impairments in the ability to inhibit responses to angry and sad faces and in the identification of happy faces compared with controls. In summer, individuals with SAD and controls performed similarly on these tasks (study 1). We also found that in summer and in winter individuals with SAD showed season-independent impairments in tasks measuring working memory, cognitive processing speed and motor speed compared to controls. Cognitive processing speed was negatively associated with the seasonal change in SAD depressive symptoms in SAD (study 2). Finally, we observed that in summer, the groups scored similarly on their personality traits, whereas in winter, individuals with SAD scored higher on Neuroticism and lower on Extraversion, compared with controls and to their own summer scores. Controls did not score any different in winter compared to summer. High scores on Neuroticism in summer were associated with more severe depressive symptoms in winter in the SAD group only (study 3).

The results obtained in this thesis suggest that impaired inhibition of angry and sad faces, reduced identification of happy faces, high levels of Neuroticism and low levels of Extraversion characterize individuals with SAD in winter compared to controls, and may thus constitute sensitive state-dependent markers of SAD pathology. Interestingly, in winter, individuals with SAD scored higher

on Neuroticism and lower on Extraversion compared to their own summer scores. One interpretation of these results is that individuals suffering from SAD, experience seasonal fluctuations at the very core of their self-perceived personality. Impaired working memory, cognitive processing- and motor speed may constitute more trait-like characteristics of SAD, as these impairments did not change as individuals with SAD moved from their depressive phase to their asymptomatic phase. Cognitive processing speed and Neuroticism appear to be related to depressive symptoms in SAD and may thus constitute SAD vulnerability trait-like markers.

Our findings provide a psychological link between cognitive mechanisms and personality characteristics and SAD. This could guide future longitudinal studies aiming to study which psychological factors are involved in the development of SAD.

DANSK RESUMÉ

De fleste mennesker tilpasser sig vinterens kulde og mørke, men omkring 12% af den københavnske befolkning oplever symptomer som er i overensstemmelse med de diagnostiske kriterier for en egentlig vinterdepression (Seasonal Affective Disorder, SAD). Vinterdepression er en tilstand med tilbagevendende depressive symptomer som tiltager i efterårs- og vintermånederne og forbedres eller remitterer fuldstændigt det følgende forår eller sommer. Man har kun delvist afdækket hvilke forhold i hjernen og ved personligheden, der er anderledes hos personer med vinterdepression. Formålet med afhandlingen var at undersøge om personer med vinterdepression adskiller sig kognitivt og personlighedsmæssigt fra raske kontrolpersoner. Vi undersøgte 29 personer diagnosticeret med vinterdepression og sammenlignede dem med 30 raske kontrolpersoner. Alle blev undersøgt neuropsykologisk og med spørgeskemaer der karakteriserede personlighed og humør, én gang om vinteren og én gang om sommeren.

Vi fandt, at personer med vinterdepression i den depressive fase havde forstyrret motorisk responshæmning ved vrede og triste ansigter og vanskeligheder med at identificere glade ansigter sammenlignet med kontrolpersonerne. I remitteret fase klarede de to grupper sig ens på disse tests (studie 1). Vi fandt desuden, at personer med vinterdepression havde svækket arbejdshukommelse, var langsommere til at bearbejde information og langsommere motorisk, både i den depressive fase og i remitteret fase. Hos personer med vinterdepression var langsom informationsbearbejdning relateret til stigning i depressive symptomer fra sommer til vinter (studie 2). Personer med vinterdepression scorede også højere på personlighedstrækket Neuroticisme og lavere på personlighedstrækket Ekstraversion i depressiv fase, både sammenlignet med kontrolpersonerne men også sammenlignet med deres egne personlighedsscores i remitteret fase. I remitteret fase fandt vi ikke personlighedsmæssige forskelle mellem grupperne. Endeligt fandt vi, at høje Neuroticisme scores i remitteret fase hos personer med vinterdepression var relateret til sværere depressive symptomer i depressiv fase (studie 3).

Disse resultater tyder på, at mens nogle kognitive vanskeligheder kun er til stede når personer med vinterdepression er depressive, optræder andre kognitive vanskeligheder både i depressiv og i remitteret fase. Desuden tyder vores resultater på, at personer med vinterdepression oplever årstidsvariationer i personlighedstrækkene Neuroticisme og Ekstraversion svarende til ændringer i deres kliniske symptomer, og at langsom informationsbearbejdning og høje Neuroticisme scores er relateret til depressive symptomer hos personer med vinterdepression. Vores fund kan

inspirere fremtidige længdesnitsundersøgelser, der har til formål at bestemme hvilke kognitive funktioner og personlighedskarakteristika, der er involveret i senere udvikling af vinterdepression.

LIST OF PAPERS

This thesis is based on the following three published studies, and are included in the appendix.

Study 1 (Paper 1)

Hjordt, L. V., Stenbaek, D. S., Madsen, K. S., Mc Mahon, B., Jensen, C. G., Vestergaard, M., Hageman, I., Meder, D., Hasselbalch, S. G., & Knudsen, G. M. (2017). State-dependent alterations in inhibitory control and emotional face identification in seasonal affective disorder. Journal Abnormal Psychology, 126(3), 291-300. doi:10.1037/abn0000251

Study 2 (Paper 2)

Hjordt, L. V., Stenbaek, D. S., Ozenne, B., Mc Mahon, B., Hageman, I., Hasselbalch, S. G., & Knudsen, G. M. (2017). Season-independent cognitive deficits in seasonal affective disorder and their relation to depressive symptoms. Psychiatry Research, 257, 219-226.

Study 3 (Paper 3)

Hjordt, L. V., Dam, V. H., Ozenne, B., Hageman, I., Mc Mahon, B., Mortensen, E. L., Knudsen, G. M., Stenbaek, D. S. (2018). Self-perceived personality characteristics in seasonal affective disorder and their implications for severity of depression. Psychiatry Research, 262, 108-114. doi:10.1016/j.psychres.2018.02.015

Selected papers

da Cunha-Bang, S.*****, **Hjordt, L. V.*,** Dam, V. H., Stenbaek, D. S., Sestoft, D., & Knudsen, G. M. (2017). Anterior cingulate serotonin 1B receptor binding is associated with emotional response inhibition. Journal of Psychiatric Reaserch, 92, 199-204. doi:10.1016/j.jpsychires.2017.05.003

da Cunha-Bang, S., **Hjordt, L. V**., Perfalk, E., Beliveau, V., Bock, C., Lehel, S., . . . Knudsen, G. M. (2017). Serotonin 1B Receptor Binding Is Associated With Trait Anger and Level of Psychopathy in Violent Offenders. Biological Psychiatry, 82(4), 267-274. doi:10.1016/j.biopsych.2016.02.030

Jensen, C. G.,*** Hjordt, L. V. *,** Stenbaek, D. S., Andersen, E., Back, S. K., Lansner, J., . . . Hasselbalch, S. G. (2016). Development and psychometric validation of the verbal affective memory test. Memory, 24(9), 1208-1223. doi:10.1080/09658211.2015.1087573

Stenbaek, D. S., **Hjordt, L. V**., Haahr, M. E., Worm, D., Hansen, D. L., Mortensen, E. L., & Knudsen, G. M. (2014). Personality characteristics in surgery seeking and non-surgery seeking obese individuals compared to non-obese controls. Eating Behavior, 15(4), 595-598. doi:10.1016/j.eatbeh.2014.08.008

* The two authors contributed equally to this work.

NOMENCLATURE AND LIST OF ABBREVIATIONS

Seasonal Affective Disorder (SAD): Depressive episodes with a winter pattern. SAD is used equivalent to the terms winter depression and seasonal depression. Subsyndromal Seasonal Affective Disorder (S-SAD): A milder form of SAD, with similar seasonal-dependent changes in mood, behaviour and vegetative symptoms, albeit not meeting the diagnostic criteria for SAD. Seasonality: The degree to which seasonal changes affect the mood, energy, sleep length, appetite, food preference, or the wish to socialize with other people. Non-seasonal depression: Major Depressive Episodes without a seasonal pattern and are equivalent to Major Depression Disorder. The terms "vulnerability and diathesis" and the terms "cognitive tests and neuropsychological tests" are employed interchangeably.

Abbreviation	*Explicated term*
ACC:	Anterior Cingulate Cortex
ANOVA	Univariate Analysis of Variance
APA:	American Psychiatric Association
ATQ:	Automatic Thoughts Questionnaire
ASQ:	Attributional Style Questionnaire
BDI:	Beck Depression Inventory
BLT:	Bright Light Therapy
BMI:	Body Mass Index
CBT:	Cognitive Behavioural Therapy
CBT-SAD:	Cognitive Behavioural Therapy tailored for SAD
CC:	Case-controlled study
CO:	Cross over study
CS:	Cross sectional study
CANTAB:	Cambridge Neuropsychological Test Automated Battery
CFQ:	Cognitive Failures Questionnaire
CI:	Confidence Interval
df:	Degrees of freedom
DAS:	Dysfunctional Attitude Scale
DER:	The Daily Emotion Records
DBPG:	Double-blind Parallel-group
DSM-V:	Diagnostic and Statistical Manual of Mental Disorders, 5th edition

DMTS:	Delayed Matching-to-Sample tests
DTW:	Dual Task Walking
EFIT:	The Emotional Identification Task
FFM:	Five Factor Model
GSS:	Global Seasonality Score
HC:	Healthy controls
ICD-10:	International Classification of Diseases, 10th revision
IS:	Intervention study
ISI:	Inter-Stimulus Interval
LNS:	Letter-Number Sequencing
MDD	Major Depressive Disorder
MDE:	Major Depressive Episodes
MDI:	Major Depression Inventory
MEY:	Multiple Errands Test
MRI:	Magnetic Resonance Imaging
MS:	Milliseconds
N:	Number of participants in a sample
NEO PI-R:	NEO Personality Inventory – Revised
NIMH:	National Institute of Mental Health
NRU:	Neurobiology Research Unit
PES	Pleasant Events Schedule
POMS:	Profile of Mood States
PS:	Prospective study
P-value:	Probability value
r_p:	Partial *r*
RDC:	Research Diagnostic Criteria
RIAS:	Reynolds Intellectual Assessment Scales
RIST:	The Reynolds Intellectual Screening Test
RSQ:	Response Styles Questionnaire
SCAN:	Schedules for Clinical Assessment in Neuropsychiatry
SAD:	Seasonal Affective Disorder
SD:	Standard deviation
SDMT:	Symbol Digit Modality Task
SMTS:	Simultaneous matching-to-sample test

SIGH-SAD:	Structured Interview Guide for the Hamilton Depression Rating Scale—Seasonal Affective Disorder
SPSS:	Statistical Package for Social Sciences
SRT:	Simple Reaction Time
SCR:	Skin Conductance Responses
S-SAD:	Subsyndromal Seasonal Affective Disorder
WRPAB:	Walter Reed Performance Assessment Battery
WHO:	World Health Organization
5-HT:	Serotonin, 5-hydroxytryptamine
5-PFs:	The Big Five Personality factors

Note: The list explains the abbreviations applied throughout the thesis

INTRODUCTION

Like the bears, squirrels, and birds, humans have evolved under the sun. We incorporated into the machinery of our bodies the rhythms of night and day, of darkness and light, of cold and warmth, of scarcity and plenty. Over hundreds of thousands of years, the architecture of our bodies has been shaped by the seasons and we have developed mechanisms to deal with the regular changes that they bring. Sometimes, however, these mechanisms break down and cause us trouble.

- Rosenthal, 2013, p. 2

INTRODUCTION TO SEASONAL AFFECTIVE DISORDER

The seasons

A season is a period of the year characterized by changes in e.g. weather conditions, temperatures, ecology, amount of daylight and length of day. The changing characteristics of each season are the results of the earth's orbit around the sun and the earth's axial tilt. In Denmark, which is situated in the northern hemisphere, there are four seasons; spring, summer, fall and winter. The four seasons vary significantly in characteristics, and prompt changes in the world around us. For example, summer brings longer, warmer and brighter days; trees and flowers bloom, the grass is bright green, and birds return filling parks with their song. The summer season also bring social activities outdoors; people visit beaches or rests in parks to unwind themselves under clear blue skies. In contrast to the summer, is the winter season. The winter brings shorter, colder and darker days. Environmental cues, such as leaves turning a simple brown, fall foliage and (some) animals migrate or go into hibernation, provides clear seasonal information about the oncoming winter. Winter typically makes people stay inside more, curse the cold and miss the summer. As such, the summer and winter season clearly affects humans in two very distinct ways.

Change of seasons and mental illness

The effects of the seasons on humans have been an on-going theme for centuries for many artists, poets and songwriters, but also the medical importance of the change of season has been well-known for centuries. For example, the observation that mental illness is sensitive to seasonal climatic conditions has been dominant in many ancient theories about the causes of illness. Hippocrates stated "*…it is chiefly the changes of the season which produce disease, and in the seasons the great change from cold or heat*" (Hippocrates, 1969 cited in Wehr and Rosenthal, 1989, p. 829). Correspondingly, the Greek Posidoius observed that mania was a recurrent illness that presented itself once a year, typically in the summer whereas melancholia presented primarily in fall. In addition, psychiatrists of the nineteenth and twentieth centuries have described patients presenting with recurrent winter depressions, e.g. Kraepelin observed that some individuals experienced depressive episodes in fall that passed over in spring (Betrus and Elmore, 1991; Magnusson and Partonen, 2010a; Wehr and Rosenthal, 1989). These historical annotations help provide a perspective for the present-day interest of the relation between the change of seasons and mood disorders.

Discovering Seasonal Affective Disorder

In 1981 a Washington Post article began: "*I should have been a bear. Bears are allowed to hibernate; humans are not*" (Quote cited in Rosenthal (2013, p. 16)). The quote came from a young woman suffering from depressions that only emerged in fall when the days got shorter. A psychiatrist named Rosenthal and his colleagues from The National Institute of Mental Health (NIMH) were studying the effect of light on mood and hypothesized that some individuals would respond negatively to the diminishing exposure to sunlight in winter. At the end of the article, the reporter asked readers to contact Rosenthal if they also experienced seasonal changes in mood. Rosenthal received over 3000 responses (Rosenthal, 2013). In 1984, he coined the term Seasonal Affective Disorder (SAD), formulated SAD diagnostic criteria and proved its validity based on its characteristic course of illness, clinical symptoms and successful treatment with bright light therapy (Rosenthal et al., 1984). While SAD is believed to represent the pathological extreme of a spectrum of seasonality, Subsyndromal SAD (S-SAD) also known as "winter-blues" is a less severe form of SAD where seasonal changes in mood or behaviour are subjectively impairing but not meeting SAD diagnostic criteria (Kasper et al., 1989). According to Rosenthal et al. (1984) the SAD diagnosis can be given if an individual fulfil all of the following criteria:

1. A history of Major Affective Disorder, according to Research Diagnostic Criteria (RDC)
2. At least two consecutive years in which the depressions have developed during fall or winter and remitted by the following spring or summer (a history of this pattern changing with changes in latitude or climate would strengthen the diagnosis)
3. Absence of any other Axis I psychiatric disorder
4. Absence of any clear-cut seasonally changing psychosocial variables that would account for the seasonal variability in mood and behaviour, e.g. work stressors

Although most people living in countries far north or south of Equator are coping well with the winter season about 12% of the population in Copenhagen meet the diagnostic criteria for SAD and about 5% experience S-SAD (Dam et al., 1998). SAD occurs four times as often in women than in men (Magnusson, 2000) and the presence of SAD is more frequent in younger adults (Magnusson and Partonen, 2010b; Swedo et al., 1995).

Clinical characteristics of SAD

The clinical characteristics of SAD pertain to symptoms also associated with non-seasonal depression, such as persistent feelings of sadness, hopelessness and inadequacy, typically leading to social withdrawal and difficulties upholding daily activities. Classic symptoms of non-seasonal

depression also include loss of interest or pleasure in activities, weight loss or gain, sleep disturbances, fatigue, psychomotor agitation or retardation, difficulties concentrating and decreased attention. Although not contained within the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) diagnostic criteria for SAD, most individuals with SAD frequently experience vegetative symptoms such as hypersomnia, increased appetite or carbohydrate craving, and weight gain (Magnusson and Partonen, 2005; Partonen and Rosenthal, 2010). Even though the depressive symptoms are rarely severe enough to cause an absence from work, many individuals with SAD experience disability in their social, professional, and psychological functioning (Pendse et al., 2003; Schlager et al., 1995). Periods of transient hypomania are frequent during summer months (Lingjaerde and Reichborn-Kjennerud, 1993) and similar to other depressive disorders, suicidal thoughts may also be present in SAD (Praschak-Rieder et al., 1997). Below follows '*A SAD story*" which is a fictive presentation of how a woman experience and battle with her SAD. The story is based on the work of Norman Rosenthal et al. 1984 and personal stories from the individuals with SAD participating in the study and is formulated in collaboration with the psychiatrists Ida Hageman and Henrik Dam at Psychiatric Centre Copenhagen.

'A SAD story'

My name is Maria and I'm 28 years old. When telling people about my SAD I describe it as my "predictable darkness" typically beginning in October and lasting until early April. By November my thinking feels pitch black. Feelings of sadness, irritability, anxiety and worthlessness are playing around in my mind, and I can't ignore them. I have trouble getting out of bed in the morning because I'm so tired, even an automatic activity such as dressing for the weather feels demanding, cumbersome and time-consuming. It is like constantly having this invisible weight on my shoulders. This tiredness together with an unexplained fatigue during the day makes me avoid many everyday activities completely in favor of staying in bed and sleep. I always try to fight the exhaustion, but sometimes it's too much though, and so my bed provides a wonderful relief. I simply don't have the energy and interest to relate to other people, not even my husband or my kids. I can't concentrate on anything; my mind feels like jelly and I'm more forgetful than ever. My colleagues have also noticed this, which worries me a lot. I also have this overwhelming craving for sweets, and I'm putting on extra kilos during the winter. I do not experience any of these problems in September. By April, my energy and positive mindset starts to return, but for almost half the year I feel like just... existing, not living…

Based on the narratives expressed by individuals suffering from SAD, and because only one out of twenty-five individuals with SAD is correctly diagnosed and thus adequately treated (Michalak et al., 2001), SAD represent a substantial public health concern, both at the economic and social level. Hence, a better understanding of this disorder is clearly relevant.

The overall aim of this thesis is to gain more knowledge on how cognitive functions and self-perceived personality traits are involved in SAD and how they associate with depressive symptoms. The 'background' section of this thesis gives a narrative overview of the distinction between trait and state factors, describes integrative approaches to study SAD, and reviews studies on cognitive, behavioural and personality factors associated with SAD. For a complete overview of studies reviewed in the 'background' section, see Table 2. This thesis is based on three published paper examining seasonal changes in: Inhibitory control and emotional face identification (study 1, paper 1), working memory, cognitive processing speed and motor speed (study 2, paper 2) and self-perceived personality characteristics (study 3, paper 3) in individuals diagnosed with SAD compared to demographically matched healthy controls. In comparison with the extensive research literature on cognitive, behavioural and personality factors in individuals with Major Depression Disorder (MDD), relatively few studies have examined such factors in SAD. Thus, results from studies on MDD will be described where appropriate.

Delimitation of the thesis

This thesis will only occasionally elucidate research on S-SAD (for a review on research on S-SAD, see Young & Yap, 2010), as well as Summer-SAD, i.e. depressive episodes occurring in the spring-summer and remission in the fall and winter (for a review on Summer-SAD see Wehr et al. (1989)) Although retinal sensitivity to light (photo-stasis), altered monoaminergic neurotransmission, and genetic polymorphisms related to serotonin or the circadian clock characterize some individuals diagnosed with SAD (thus pointing to the relevance of these factors in the etiology of SAD) they will not be discussed in this thesis. The reader who wish to know more about these subjects are referred to the following papers Hébert (2010); Mc Mahon et al. (2016); Melrose (2015); Praschak-Rieder and Willeit (2012); Rosenthal et al. (1998); Sahar and Sassone-Corsi (2010). The treatment options for SAD, which typically include Bright Light Therapy (BLT), antidepressant medications, Cognitive Behavioural Therapy (CBT), Cognitive Behavioural Therapy tailored for SAD (CBT-SAD), or therapeutic counselling are not discussed in this thesis. For therapeutic options for SAD: Golden et al. (2005); Melrose (2015); Rohan et al. (2010); Rohan et al. (2016); Winkler et al. (2006); Winkler et al. (2010).

BACKGROUND

Whoever wishes to pursue the science of medicine in a direct manner must first investigate the seasons of the year and what occurs in them.

- Hippocrates

BACKGROUND

SAD — A highly complex phenomenon?

For several decades, SAD was primarily considered a consequence of seasonal changes in biorhythms, in particular circadian misalignment of melatonin secretion (Brown et al., 2010; Lewy et al., 1980), triggered by reduced light availability in winter. Hence, treating individuals with SAD, was for many years, though to be quite straightforward: Daily use of BLT in winter would make SAD depressive symptoms disappear (Rosenthal et al., 1984). Unfortunately, the etiology of SAD has proven to be more complex resulting from dynamic interactions of several vulnerability factors, as some individuals with SAD do not benefit from BLT and no purely biological explanation have been found to fully account for the SAD development. Although it is generally acknowledged that SAD is a multifaceted phenomenon (Rohan et al., 2009; Young and Yap, 2010), it is not well elucidated how and which psychological factors are involved in SAD, which is arguably important for a better understanding of the disorder.

Trait, state and vulnerability factors

An important conceptual and empirical advance for research on vulnerability to psychopathology (and SAD) has been the distinction between trait, state and vulnerability factors. In a SAD context, traits refer to relative stable individual dispositions that are evident before and during the SAD depressive episode. Thus, being stable over time, traits cannot themselves cause the onset of a depressive episode, but may indicate an underlying vulnerability. Despite the extensive discussions about vulnerability traits within the research literature, the term is not clearly defined, but commonly, vulnerability is considered as a pre-existing trait, that is stable, but not unchangeable. For example, change may be possible if the level of vulnerability is psychological rather than e.g. genetic, and therapy is based on just this belief. Vulnerability is also considered endogenous to individuals, is usually latent and increases the susceptibility to the occurrence of psychopathology most often in the context of a stressor (Ingram et al., 2011; Ingram and Luxton, 2005, p. 34). Traits may also affect the clinical features, severity, course, or maintenance of a depressive episode. Alternatively, traits may after recovery from a depressive episode, reflect a scar (i.e., persistent cognitive changes resulting from the depression) (Christesen and Kessing, 2006; Lewinsohn et al., 1981). State markers, on the other hand, represent clinical appearances that are temporary and only present while the individual is currently depressed.

Because individuals with SAD experience a predictable pattern of depressive episodes in the fall/winter and full remissions in the spring/summer, SAD serve as a *natural depression model* to separate trait-like from state markers. Disentangling trait-like from state markers of SAD necessitate longitudinal study designs with currently depressed and remitted individuals with SAD and demographically matched healthy controls. Unfortunately, most available research on SAD has been single, as opposed to repeated assessment, and hence has only established that relationships between traits and SAD exist.

Vulnerability-stress models of SAD

Vulnerability-stress model considers psychiatric disorders as the result of the interaction between an individual's vulnerability for a disorder and a stressor (Ingram and Luxton, 2005), hence vulnerability factors are fundamental in these models. The majority of theories of SAD are vulnerability-stress models emphasizing that a seasonally varying environmental stressor, most likely related to change in day and night cycle and/or natural light availability (e.g. short photoperiod, later dawns, reduced overall natural light availability) (Rohan et al., 2009), that interacts with predisposed vulnerabilities and induces the regular recurrences of SAD depressive symptoms, observed in some individuals during winter months (McCarthy et al., 2002; Young and Yap, 2010). The few empirical studies that have investigated the association between these seasonally varying environmental stressors and SAD point to short photoperiod or sunshine duration as key stressors in SAD onset (Sarran et al., 2017) and depression severity (Molin et al., 1996; Oren et al., 1994; Young et al., 1997). However, recently a large cross-sectional U.S. survey of 1.754 adults who met the criteria for depression on the Patient Health Questionnaire-8 failed to demonstrate that depression was related to latitude, season, or sunlight (Traffanstedt et al., 2016), thus questioning previous findings on photoperiod and sunshine as salient environmental stressors of SAD, thereby bringing into question SAD as being a distinct disorder.

Young's Dual-Vulnerability Model of SAD

Converging evidence supports the role of cognitive, behavioural and personality factors in SAD (Young and Yap, 2010). Young et al. (1991) were the first to suggest psychological factors as vulnerabilities in SAD. The Dual Vulnerability Model of SAD first suggested by Young et al. (1991) and elaborated by Lam et al. (2001) proposes that two vulnerabilities are involved in the development of SAD: 1) a primary physiological vegetative response (e.g. hypersomnia, hyperphagia, and low energy) to seasonal environmental changes and 2) a secondary cognitive-affective response to these vegetative changes based on psychological depressive vulnerabilities. In this context, the vegetative

change functions act as a stressor that triggers the underlying psychological vulnerability to develop cognitive and affective symptoms. Consequently, cognitive and affective symptoms occur after the onset of vegetative symptoms in individuals with the psychological vulnerability, which has been supported in several studies showing (McCarthy et al., 2002; Whitcomb-Smith et al., 2014; Young et al., 1991).

Rohan's Integrated Cognitive-Behavioural model of SAD

In extension of Young's Dual Vulnerability model, Rohan (2009) proposed the Integrated Cognitive-Behavioural model of SAD to show how psychological, behavioural and physiological vulnerabilities have etiological importance for SAD onset, maintenance and remission (see Figure 1). This latter model also proposes that two vulnerabilities are involved in the SAD etiology: 1) a genetically-mediated physiological vulnerability and 2) a psychological vulnerability. According to the model the development of SAD occurs when there is a substantial environmental stressor (e.g. decreasing photoperiod or cues that mark changes from summer to winter such as leaves turning brown) that triggers a reverberating cycle between psychological (e.g. dysfunctional attitudes or behavioural disengagement) and physiological vulnerabilities (e.g. serotonin dysfunction or circadian phase-shift) and/or when negative expectations about the impending winter triggers a psychological vulnerability, which, in turn, triggers the physiological vulnerability (Rohan, 2009, p. 5). Without treatment, the SAD depressive episode will remit when the environmental stressor changes significantly (e.g. increasing photoperiod or cues that mark the coming of spring) and deactivates both vulnerabilities or when positive expectations about the spring deactivate the psychological vulnerability, which, in turn, deactivates the physiological vulnerability (Rohan et al., 2009, p. 44). In contrast to the Dual Vulnerability model, the Integrated Cognitive-Behavioural model of SAD explicitly points to which psychological and biological factors may constitute a vulnerability to SAD. The psychological vulnerabilities include maladaptive schemas, attitudes, automatic thoughts and ruminative thinking resembling those seen in non-seasonal depression, but also involve behavioural factors including low rate of response-contingent positive reinforcement, as well as learned emotional and psychophysiological reactivity to low light- and winter-related stimuli (Rohan, 2009). Although both models are somewhat simplified, it may serve to bridge the gap between psychological and biological approaches to study SAD or guide future intervention studies.

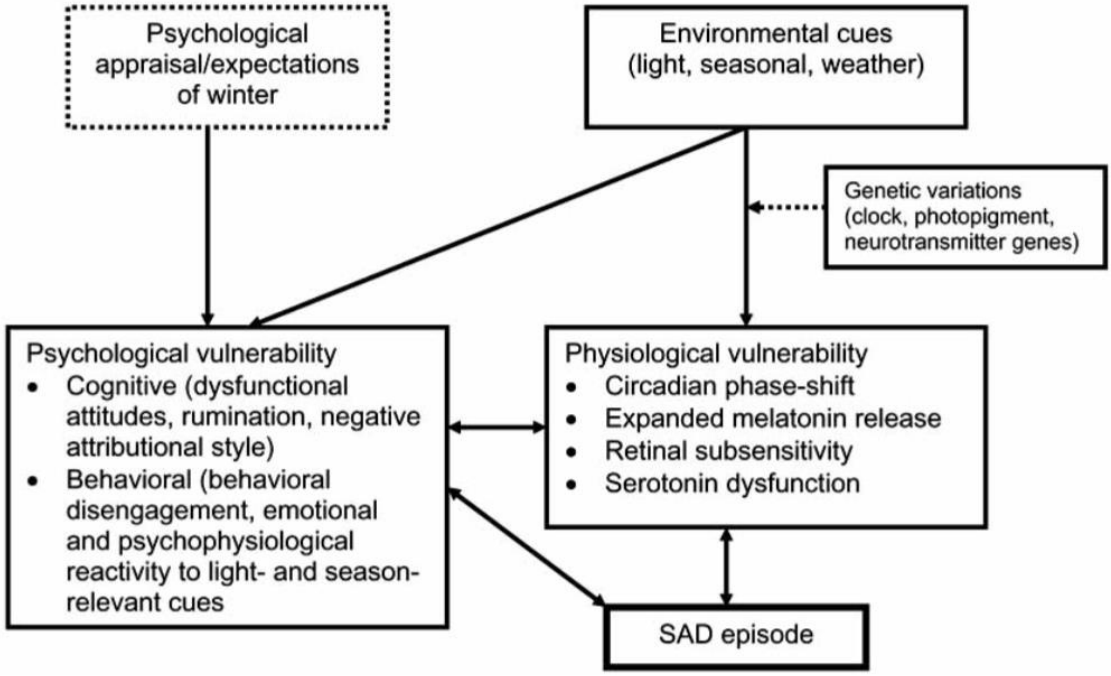

Figure 1. The Integrative Cognitive-Behavioural model of Seasonal Affective Disorder (SAD) by (Rohan et al., 2009).

In the following sections, studies on cognitive, behavioural and personality factors associated with SAD are reviewed.

Cognition in SAD

DSM-V describes MDD as a psychiatric disorder with cognitive symptoms, underscored by their presence in the diagnostic criteria for a Major Depressive Episode (MDE) (APA, 2013). MDD related cognitive impairments can be observed in several cognitive domains, including attention, working memory, processing speed (Buthmann et al., 2016). Individuals with MDD also show a bias towards processing of negative information and/or away from positive information (Elliott et al., 2011). The cognitive symptoms related to MDD and SAD contribute significantly to the disabling effects that these disorders are shown to have on social and professional functioning (Buthmann et al., 2016; Greer and Hatt, 2016; Pendse et al., 2003; Schlager et al., 1995). Cognitive functions can broadly be divided into 'hot' and 'cold' cognition. This distinction infers that cognitive functions may operate differently in different contexts. Whereas hot cognition involves affective information and describes affectively valenced cognitive processing, cold cognition involves non-affective information and describes non-affectively valenced cognitive processing (Robinson et al., 2016). As suggested by Robinson et al. (2016) hot cognitive biases can also be observed in cold cognitive test, especially if individuals are provided with feedback. For example, it has been demonstrated that depressed

individuals tend to demonstrate a "*catastrophic response to perceived failure*" (Robinson et al., 2016, p. 72). Both hot and cold cognitive symptoms are hypothesized to be involved in the etiology of MDD promoting, sustaining or worsening the negative emotional state by e.g. facilitating the development of negative self-scheme and rumination (Beck, 1967; Buthmann et al., 2016; Lam et al., 2001; Robinson et al., 2016; Young et al., 2008; Young et al., 1991). Studies also suggest hot and cold cognition are of relevance for SAD etiology (for a review see Rohan et al. (2009)).

Previous studies examining cognition in SAD have mostly relied on self-report methods and only a handful of studies have used neuropsychological tests. Although both methods have the advantage of associating mood and cognition, self-report cognitive measurements may be more susceptible to response biases (Domino, 2006) compared to neuropsychological measurements that allows for more objective and detailed analyses of hot and cold cognitive functions (Lezak, 2012). In the following, cognitive and behavioural factors are reviewed as mechanisms relevant for SAD etiology, through their potential interacting with biological mechanisms to develop SAD.

Hot cognition

Biases in hot cognition are typically measured with neuropsychological tests in which affective information should be attended to, perceived, remembered or inhibited (Elliott et al., 2011), but may also include self-reportable cognitive constructs such as dysfunctional attitudes and negative ruminative thinking. Currently depressed individuals with MDD often present with biases in hot cognition, such as negative ruminative thinking (Nolen-Hoeksema et al., 2008), catastrophic responses (Robinson et al., 2016) and an increased processing of negatively valenced information and/or reduced processing of positively valenced information (Elliott et al., 2011; Roiser and Sahakian, 2013), Although most studies on MDD report the presence of affective biases during the depressed state, is less clear whether they are reversible after remission (Miskowiak and Carvalho, 2014; Robinson et al., 2016), leaving it inconclusive whether biases in hot cognition act as state or trait dependent characteristics of MDD. Interestingly, subtle, hot cognitive biases have been observed in healthy relatives to individuals with MDD, raising the possibility that they may represent underlying vulnerability traits to depression (Mathews and MacLeod, 2005; Miskowiak and Carvalho, 2014).

Hot cognition in SAD: Measured with neuropsychological tests

The studies that have examined hot cognition in SAD using neuropsychological tests point to affective biases at different levels of information processing. For example, three studies have

examined attentional bias in SAD (Harmer et al., 2012; Sigmon et al., 2007b; Spinks and Dalgleish, 2001). Sigmon et al. (2007b) found that individuals with SAD during symptomatic phase were slower to color name seasonal-related words (e.g. dark) and depressive words (e.g. hopeless) on a modified emotional stroop tasks compared to controls. Correspondently, in an intervention study, Harmer et al. (2012) found that under baseline conditions, individuals with SAD and S-SAD showed increased vigilance to negative versus positive items on an emotional dot-probe task compared to controls. In an uncontrolled study, Spinks and Dalgleish (2001) examined attentional bias across season in individuals with SAD using a modified emotional stroop task and found that SAD was associated with longer response times to colour name seasonal and negative words in both summer and winter. Since the later study did not include a control group, it remains unknown whether attentional bias represent a trait or a state characteristics of SAD. Rohan et al. (2004) examined individuals with S-SAD and controls in winter and in non-winter months (September or April) on a modified emotional stroop task using light-related words, and did not find any group differences across season. A possible interpretation across these studies is that a negative attentional bias towards negative stimuli appears more state dependent in SAD.

Four studies have examined affective memory in SAD (Dalgleish et al., 2004; Dalgleish et al., 2001; Harmer et al., 2012; Jensen et al., 2015). Jensen et al. (2015) found that individuals with SAD exhibit a larger winter-associated decline in recall of positive words compared with healthy controls, which also correlated significantly with the increase in SAD specific symptoms from summer to winter. Corroborating this, currently depressed individuals with SAD endorsed more negative words and fever positive words as self-referent words compared to controls (Dalgleish et al., 2004). In addition, individuals with SAD and S-SAD showed a reduced recall of positive versus negative personality characteristics and an increased recognition of negative versus positive self-referent words compared to controls (Harmer et al., 2012). Dalgleish et al. (2001) found that individuals with SAD did not show elevated recall of overgeneral memories to positive cues (i.e. the tendency to recall fewer specific memories and instead produce general memories of past events (Gibbs and Rude, 2004)) relative to controls, but that the absolute level of general memories to positive cues was associated with more severe depressive symptoms during remission. These results on affective memory as a whole indicate reduced memory for positive information and/or increased memory for negative information in SAD during winter.

Finally, misinterpretation of social affective cues, may be related to the social deficits, characterizing some individuals with SAD. Interestingly, reduced recognition of positive facial expressions has been found in individuals with SAD and S-SAD relative to controls, when examined in winter during a control baseline condition (Harmer et al., 2012).

Hot cognition in SAD: Measured with self-report instruments

Most SAD research on hot cognition has relied on self-report questionnaires and has focused on cognitive constructs that are typically considered vulnerabilities for depression including negative attributional style[1] (Abramson et al., 1989), dysfunctional attitudes[2] (Beck, 1976), and rumination[3] (Nolen-Hoeksema, 1991). These cognitive constructs associated with MDD also are operative in SAD. For example, in cross-sectional studies currently depressed individuals with SAD, reported higher levels of negative attributional styles (Dalgleish et al., 2004) and dysfunctional attitudes (Golden et al., 2006; Hodges & Marks, 1998) compared to healthy controls. Two studies have failed to find support of dysfunctional attitudes as a state marker of SAD (Rohan et al., 2003; Sigmon et al., 2007b); Sigmon et al. (2007b) found no differences between SAD and healthy controls in dysfunctional attitudes in winter. Correspondingly, Rohan et al. (2003) examined dysfunctional attitudes longitudinally, and found that SAD and healthy controls did not differ in levels of dysfunctional attitudes in fall, winter and summer. Importantly, none of the above studies on dysfunctional attitudes included a mood induction, which has been recommended in order to use dysfunctional attitude measurements as a vulnerability measure. Only one study has examined dysfunctional attitudes under mood induction and found that higher levels of dysfunctional attitudes were associated with greater depressed mood when measured retrospectively (i.e. what the participants typically experienced during winter) and prospectively the following winter (Enggasser and Young, 2007), suggesting dysfunctional attitude may be trait markers of SAD.

Individuals with SAD also report higher levels of negative automatic thoughts[4] during a depressive episode (Hodges and Marks, 1998), this is also supported by a prospective SAD study, which found higher levels of negative automatic thoughts in individuals with SAD than that of controls across the seasons (Rohan et al., 2003). Interestingly, individuals with S-SAD endorsed greater automatic negative thoughts frequency across season (Rohan et al., 2004), suggesting that negative automatic thoughts may be trait markers of SAD.

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[1] Negative attributional style: i.e., the tendency to attribute negative events to internal, stable and global causes and infer that negative events will to lead to other negative outcomes (Abramson et al., 1989, p. 358). Negative attributional style is measured with Attributional Style Questionnaire (ASQ).

[2] Dysfunctional attitudes; i.e. learned rules or assumptions that are triggered by underlying schemes guiding negative automatic thinking (Beck 1976). Dysfunctional attitudes are measured with Dysfunctional Attitudes Scale (DAS)

[3] Negative Ruminative thinking; i.e. the tendency to continually focus attention on depressive mood and its causes and consequences (Nolen-Hoeksema, 1991). Negative Ruminative thinking is measured with Response Style Questionnaire (RSQ) or Daily Emotion Records (DER)

[4] Negative Automatic Thoughts; Measured with Automatic Thoughts Questionnaire (ATQ).

Empirically, ruminative response style is the most convincing psychological vulnerability trait in SAD. Three longitudinal studies provide evidence that ruminative response style measured in summer (Enggasser and Young, 2007) or in fall (Rohan et al., 2003; Young and Azam, 2003) predict the severity of depressive symptoms in winter. Rohan et al. (2003) also showed a higher degree of rumination across season compared to healthy controls.

Behavioural disengagement in SAD

Another line of SAD research has focused on behavioural disengagement i.e., social withdrawal and low rates of positive reinforcements or pleasant events. Based on the hypotheses that behavioural disengagement contributes to depression onset or maintenance, it can be argued that behavioural disengagement may be especially important for SAD etiology, as possible positive reinforcers (e.g. outdoor activities) are low during winter, and thereby making individuals vulnerable to SAD more prone to drifting further into withdrawal during winter. Corroborating this hypothesis, women with SAD engage in fewer activities in winter compared to summer relative to controls and they report them as more enjoyable[5] in summer compared to fall or winter, suggesting that winter represent a low point in regard to activity frequency and enjoyment for individuals with SAD (Rohan et al., 2003). It remains to be clarified, whether behavioural disengagement is a consequence of decreased energy and increased fatigability, which characterize SAD and/or directly triggers the development of SAD and/or are involved in the maintenance of the disorder.

Emotional and psycho-physiological reactivity in SAD

Rohan et al. (2004) hypothesized that due to the repeated associations between low light conditions during the winter and depressive episodes in individuals with SAD, environmental cues signaling low light availability may become conditioned stimuli for eliciting negative emotional states, leaving individuals with SAD more vulnerable to develop future depressions in winter. Increased emotional and/or psycho-physiological reactivity to winter-related stimuli in SAD compared to healthy controls have been supported in four studies (Lindsey et al., 2011; Rohan et al., 2003; Rohan et al., 2004; Sigmon et al., 2007a); Rohan et al. (2003) found a cross-seasonal (winter, fall and summer) pattern of greater depressive mood when exposed to overcast sky scenes compared to bright scenes showing a clear, sunny sky. Sigmon et al. (2007a) found an increased physiological skin response and greater exacerbation of depressed mood to videos of winter scenes compared to summer scenes in SAD.

[5] Behavioural disengagement was measured with Pleasant Events Schedule (PES)

Similarly, Lindsey et al. (2011) found increased physiological skin responses and greater depressive mood when exposed to overcast stimuli compared to controls. Finally, women with S-SAD also showed a greater psycho-physiological arousal to overcast stimuli in winter relative to controls (Rohan et al., 2004). These results suggest that seasonal-related stimuli appear to have a subtle mood reducing effect on individuals with SAD. Moreover, individuals with clinical and subclinical levels of SAD appear to exhibit emotional and psychophysiological arousal to winter-related stimuli, suggesting that emotional and psycho-physiological reactivity may represent trait characteristics of SAD, but the results also raise the possibility that increased psychophysiological reactivity to winter-related stimuli constitute a vulnerability to the development of SAD.

Cold cognition

In individuals with MDD, cold cognitive impairments in executive functions, memory and attention, seem to be reliably present both during a depressive episode and during remission (Rock et al., 2014), and may represent trait markers tracking underlying vulnerability of MDD. Compared to biases in hot cognition, these cold cognitive impairments have a particular negative influence on everyday-life and professional functioning in these individuals (Buthmann et al., 2016). Typically, cold cognition is examined with neuropsychological tests where non-affective information should be remembered (e.g. list of neutral words or numbers), reacted to (e.g. reaction times towards geometric figures) or correctly sorted (e.g. based on changing sorting criteria).

Cold cognition in SAD: Measured with neuropsychological and self-report instruments

Only a handful of studies have examined cold cognition in SAD with neuropsychological tests (Drake et al., 1996; Michalon et al., 1997; O'Brien et al., 1993) and to the best of my knowledge only one study has used self-report questionnaire to examine cold cognitive processes (Michalon et al., 1997). O'Brien et al. (1993) examined individuals with SAD and healthy controls on several cold cognitive tests and found impairments in spatial memory, visual learning and processing speed during depression compared to controls. Whereas improvement was observed for all tests increased spatial memory latency was still present on recovery from depression. Drake et al. (1996) did not observe any recognition memory or attentional deficits in individuals with SAD compared to healthy controls in either summer or winter. Michalon et al. (1997) systematically administered a number of cold cognitive tests measuring general cognitive ability, attention, verbal memory, visual memory, visual construction and perception to 30 individuals with SAD and 29 matched healthy controls in winter. Consistent with the results of O'Brien et al. (1993) impairments on tests measuring visual memory and visual were observed for individuals with SAD during a depressive episode compared

to controls. A subgroup of this sample (n=13) was also assessed in summer and the impairments in visual memory and visual construction were still present. Finally, Michalon et al. (1997) also administered the self-report Cognitive failures questionnaire (CFQ) to test autobiographic memory and found that deficits in cognitive failures were present in winter but appeared at normal levels in summer.

In summary, relevant factors for the study of SAD may include impairments in different levels of information processing (i.e., attention, memory and emotional face identification), cognitive constructs typically perceived as vulnerabilities for non-seasonal depression (i.e., dysfunctional attitudes, negative attributional style, negative automatic thinking and negative ruminative), behavioural disengagement as well as increased emotional and psycho-physiological reactivity to winter-related stimuli. Although it is unknown how these cognitive impairments and biased behaviours relate to SAD onset and maintenance, they may at the very least represent correlates of SAD and more prospective longitudinal studies are needed.

Personality

Recent research on MDD has focused great attention on examining personality traits with the hypothesis that they are relevant for the organization of affective and cognitive processes (Klein et al., 2011). Thus, tracing associations between personality and depressive disorders may help elucidate etiological processes involved in the development of depression and to identify at-risk individuals. The study of SAD and personality, have mostly relied on the Five-Factor Model (FFM) of personality proposed by (McCrae and Costa, 2003). The FFM takes a trait theoretical perspective on personality and has gained wide acceptance because of its converging evidence regarding stability, heritability, consensual validation, cross-cultural invariance, and predictive utility (Costa and McCrae, 1985; Ozer and Benet-Martinez, 2006). The FFM consider personality as being relative stable individual characteristics that is ordered hierarchically with five broad global personality factors: Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness, where each factor (from now referred to as trait) is constituted by six narrow lower-order sub-facets (Costa and McCrae, 1995) (see Table 1).

Table 1: Factor structure of the personality traits and sub-facets in the FFM

Neuroticism	**Extraversion**	**Openness**
Anxiety	Warmth	Fantasy
Angry Hostility	Gregariousness	Aesthetics
Depression	Assertiveness	Feelings
Self-conscientiousness	Activity	Actions
Impulsivity	Excitement Seeking	Ideas
Vulnerability	Positive Emotions	Values
Agreeableness	**Conscientiousness**	
Trust	Competence	
Straightforwardness	Order	
Altruism	Dutifulness	
Compliance	Achievement Striving	
Modesty	Self-Discipline	
Tender-mindedness	Deliberation	

The FFM conceptualize personality traits in dimensional terms, meaning that personality varies along a continuum, signifying the degree to which individuals display different traits and can be measured with the self-reported NEO Personality Inventory - Revised (NEO PI-R). This relies on the assumption that these five traits are normally distributed in the general population. Of the five major traits presented in Figure 2, high levels of the personality trait Neuroticism are known as a putative vulnerability factor of MDD (Christesen and Kessing, 2006; Enns and Cox, 1997; Kotov et al., 2010; Malouff et al., 2005), and may influence the severity of depressive symptoms (Brown and Rosellini, 2011).

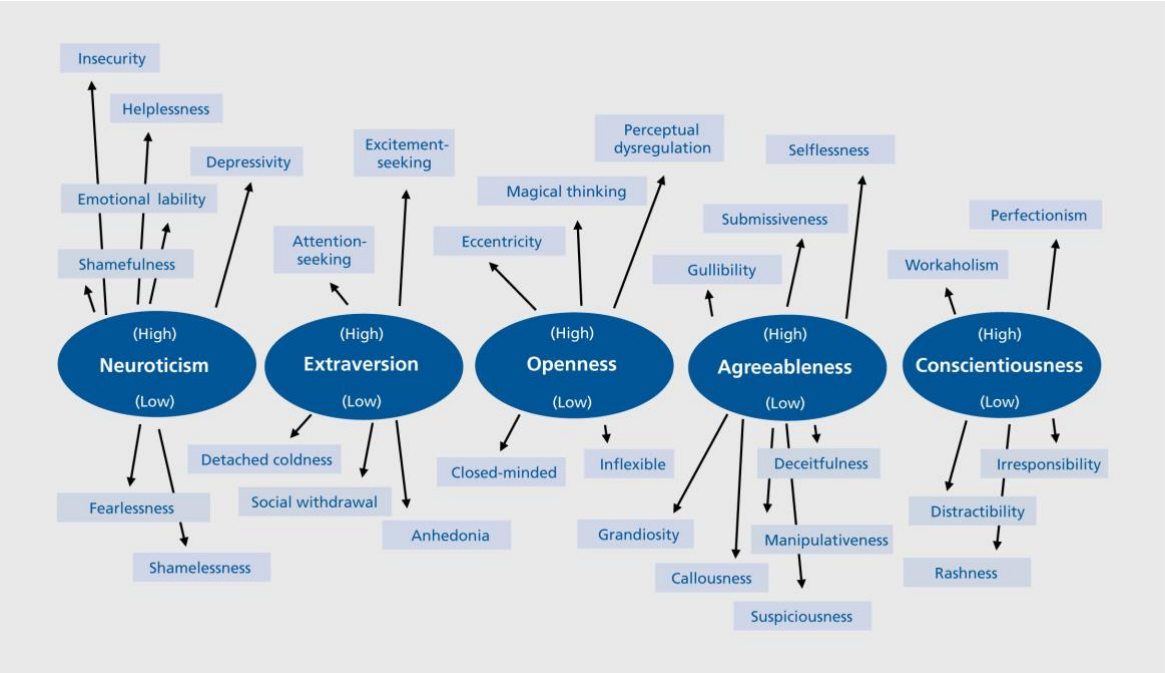

Figure 2. Examples of high and low levels of each of the five FFM traits. Figure taken from Trull and Widiger (2013).

Personality characteristics in SAD

Personality factors have also been implicated in SAD. When comparing individuals with SAD to general population norms or healthy references samples, SAD is associated with a cross-seasonal pattern of higher scores on Neuroticism (Enns et al., 2006; Gordon et al., 1999; Lingjaerde et al., 2001), higher scores on Openness (Enns et al., 2006; Gordon et al., 1999), and lower scores on Extraversion (Enns et al., 2006; Lingjaerde et al., 2001). The finding of higher scores on trait Openness is noteworthy, since trait Openness otherwise is the FFM trait least associated with risk of psychopathology (Kotov et al., 2010; Malouff et al., 2005). Only one study has examined personality characteristics in individuals with SAD longitudinally from summer to winter, and found that while scores on Neuroticism increased, Extraversion, Openness, and Conscientiousness all decreased (Enns et al., 2006). These results suggest that individuals diagnosed with SAD experience seasonal changes in their self-perceived mind. While Neuroticism also appears to be a vulnerability factor in SAD (Young and Yap, 2010), is not known whether Neuroticism during remission is associated with depression severity during the acute phase of SAD. Tracing such an association may help elucidate how personality processes are involved in SAD symptomatology and severity and help identify at-risk individuals and thus potentially offer early treatment of SAD.

However, some methodological issues in regard to the existing studies on cognition, behaviour and personality are typically hampered by one or more methodological limitations. For example, the confounding effects of psychotropic drugs or BLT, small sample sizes, cross-sectional study design, not adjusting for confounding variables such as Intelligence Quotient (IQ), lack of control groups, comparing SAD groups to unmatched controls groups, or population norm data may bias actual group differences. Groups that are not counterbalanced in regard to time of first examination may also influence the psychological constructs addressed in the studies (Rosenblat et al., 2015; Wingo et al., 2009). As such, longitudinal study designs with medication-free individuals with SAD and demographically matched healthy controls and correcting for relevant covariates are necessary to address whether hot and cold cognitive impairments observed during a depressive episode disappear or persists during remission and to examine how personality traits are implicated in SAD.

Table 2, present an overview of studies investigating hot and cold cognition, behavioural disengagement, emotional and psycho-physiological reactivity and personality in individuals with SAD.

Table 2: The table shows an overview of studies investigating psychological factors in individuals with SAD

Hot cognition (Neuropsychological measurement)					
Citation/year	**Groups/ sample size**	**Design**	**Outcome measures (*and instruments*)**	**Time of Measurement**	**Primary findings**
Dalgleish et al. 2001	SAD, n=15, HC, n=15	CC / PS	Affective memory (*Autobiographical Memory Test*)	November-December and June-July	No group differences in the recall of overgeneral memories. In SAD, absolute levels of memory to positive cue words measured in winter predicted depression scores in the summer.
Dalgleish et al. 2004	SAD, n=21, HC, n=20	CC / PS	Affective memory (*Adjective endorsement and recall task*)	November-December and June-July	SAD ↑ endorsement of negative words as self-referent and ↓ positive words as self-referent compared to controls.
Harmer et al. 2012	SAD and S-SAD, n=21 HC, n=21	IS / DBPG	Attentional bias (*Visual dot-probe task*) / Affective memory (*Emotional categorization and memory tasks)* / Emotional face identification (*Facial expression recognition*)	October-March	Control baseline condition: relative to controls, SAD and S-SAD ↑ increased vigilance to negative vs. positive words, ↑ tendency to reduced recall of positive vs. negative personality characteristics, ↑ recognition memory for negative vs. positive personality characteristics, ↓recognition of happy facial expressions relative to controls.
Jensen et al. 2015	SAD, n=28, HC, n=30	PS / CS	Verbal affective memory (*Verbal Affective Memory Test-24 (VAMT-24*))	November-January	SAD ↑ winter-associated decline in recall of positive words compared to controls, and this correlated significantly with an increase in SAD specific symptoms from summer to winter.
Rohan et al. 2004	S-SAD, n=24 women HC, n=20	CC / PS	Attention *(Modified Emotional Stroop Task)*	January-February and September or April	No group differences in cognitive interference to light-relevant words.
Sigmon et al. 2007	n= 15, SAD n= 15, MDD n= 15, HC	CC/ CS	Attention bias (*Modified Emotional Stroop task*)	January-February	SAD ↑ Reaction times to colour name dark and depressive words compared to controls.

Spinks & Dalgleish 2001	SAD, n=21 Uncontrolled	PS	Attentional bias (*Modified Emotional Stroop task*)	November-December and June-July	SAD ↑ Reaction times to name seasonal and negative words compared to neutral words and 0's in winter and summer. No seasonal change in reactions times.
Hot cognition (Self-report measurement)					
Dalgleish et al. 2004	N=21, SAD n=20, HC	CC / CS	Negative attributional style (*ASQ*)	November-December and June-July	SAD ↑ negative attributional style compared to controls and DAS scores were significantly ↑ in winter than in summer in SAD.
Engasser & Young 2007	SAD and S-SAD, n=59 (n=27 at follow-up assessment) Uncontrolled	IS (mood induction) / PS,	Dysfunctional attitudes (*DAS)* / Rumination *(RSQ)*	May- August and February	SAD ↑ dysfunctional attitudes and rumination predicted levels of depressive mood when depressed, both when dysfunctional attitudes were measured retrospectively in summer and prospectively in winter.
Golden et al. 2006	SAD, n=13 HC, n=20	CS, PS	Dysfunctional attitudes (*DAS*)	November-December	SAD ↑ dysfunctional attitudes relative to controls.
Hodges & Marks 1998	SAD, n=10 MDD, n=11 HC, n=10	CC / CS	Dysfunctional attitudes (*DAS*) / Negative Automatic Thoughts (*ATQ*)	January-February	SAD ↑ higher levels of dysfunctional attitudes and negative automatic thoughts compared to controls.
Rohan et al. 2003	SAD, n= 20 women HC, n=18	CC / PS	Dysfunctional attitudes (*DAS*) / Negative Automatic Thoughts (*ATQ*) / Rumination (*RSQ*)	October-November (fall), January-February (winter) and June-July (summer)	SAD and HC did not differ in dysfunctional attitudes during any season, but the SAD group endorsed ↑ dysfunctional attitudes in fall and winter than in summer. SAD ↑ negative automatic thoughts across season relative to controls and ↑ negative automatic thoughts in winter than in fall or summer. SAD ↑ruminative response style in fall compared to controls and fall rumination predicted symptom severity during winter.

Rohan et al. 2004	S-SAD, n= 24 women HC, n= 20	CC / PS	Negative Automatic Thoughts (*ATQ*)	January-February and September or April	S-SAD ↑ automatic negative thoughts frequency in winter and non-winter months.
Sigmon et al. 2007	SAD, n= 15, MDD, n=15 HC, n=15	CC / CS	Negative Automatic Thoughts (*ATQ*) / Rumination *(RSQ*) / Dysfunctional attitudes (*DAS)*	January-February	SAD ↑ rumination and negative automatic thoughts compared to controls. SAD and healthy controls were no different in dysfunctional attitudes in winter.
Young & Azam 2003	SAD, n=18 Uncontrolled	PS	Rumination (*DER*)	September-November and January-February	SAD ↑ fall rumination predicted symptoms severity in winter.
Behavioural disengagement and emotional and psycho-physiological reactivity					
Lindsey et al. 2011	SAD, n=24 HC, n=24	CC / CS	Emotional sensitivity to light and seasonal-related cues (*Psychophysiological task*)	During depressive episode (months not specified)	SAD ↑ physiological skin responses, and ↑ self-reported depressed mood when exposed to overcast stimuli compared to controls.
Rohan et al. 2003	SAD, n=20 women HC, n=18	CC / PS	Activity frequency and enjoyment (*PES*) / Mood (*POMS*) / Reactivity to light and dark visual stimuli (*Rohan et al.'s psychophysiological slide task)*	October-November, January-February and June-July	SAD ↓activities and ↓ active in winter compared to fall and summer. SAD ↑ enjoyment from activities in summer relative to fall and winter. SAD ↑ baseline depressed mood following presentation of low light pictures relative to bright pictures across season. No group differences were observed in psycho-physiological responses to light and dark stimuli.
Sigmon et al. 2007	SAD, n= 15, MDD, n=15 HC, n=15	CC / PS	Psychophysiological equipment recording SCR	January-February	SAD ↑ greater physiological skin response and exacerbation of depressed mood to videos of winter scenes compared to summer scenes.

Rohan et al. 2004	S-SAD, n=24 women HC, n=20	CC / PS	Reactivity to light and dark visual stimuli (*Rohan et al.'s psychophysiological slide task*)	January-February and September or April	S-SAD individuals displayed greater SCR to low light pictures relative to bright light pictures and ambiguous light pictures compared to controls.
Cold Cognition (Neuropsychological and self-report measurements)					
O'Brien et al. 1993	SAD, n= 11 HC, n=10	CC / PS	Several cold cognitive tests assessing e.g. recognition (*Pattern recognition test*), spatial memory (*Spatial recognition test*), visual attention and discrimination (SMTS), visual short-term memory (SMTS), visual learning (*Paired associate learning test*)	Winter and summer (months not specified)	SAD ↓ number of correct responses on the Spatial recognition test and on the paired associate learning test, ↑ reaction times to respond on the spatial and pattern recognition tests and on DMTS in winter compared to controls. SAD ↑ reaction times respond on the spatial pattern recognition test in summer compared to controls. No group differences were observed in summer on the paired associate learning test, the pattern recognition tests and on DMTS.
Michalon et al. 1997	SAD, n= 30 (n=13 at follow-up assessment in summer) HC, n=29	CC / IS / PS (before treatment and after treatment)	Several cold cognitive tests assessing e.g. attention (*Mental control, Digit Symbol, Digit span and stroop colour-word test*), verbal memory (*Logical memory - immediate and delayed recall, recognition memory for words*), visual memory (*Recognition memory for faces, Rey Complex Figure Delayed Recall test*), visual construction/ perception (*Rey Complex Figure Copy, Block design, Facial Recognition*), language (*Fluency, letter and semantic categories*) and motor speed (*finger tapping*)**.** Everyday slips or errors (CFQ)	Winter and summer (months not specified)	SAD ↓ scores on Recognition of memory for faces, Rey Complex Figure Delayed recall test and Rey Complex Figure Delayed copy in winter compared to controls. Scores on Rey Complex Figure Delayed recall test and Rey Complex Figure Delayed copy remained low in summer. SAD ↑ CFQ scores compared to controls in winter.

Drake et al. (1996)	SAD, n= 10 HC, n=9	CC / PS	Attention (*Stroop Task*) and recognition memory (*Pattern recognition task from the WRPAB*)	Summer and winter (months not specified)	No group differences in Stroop or Pattern recognition performance in either summer or winter. All study participants performed better on the Stroop task in summer compared to winter.
Personality					
Enns et al. 2006	SAD, n=64 Published normative data, n=1000	CS /IS / PS	Personality (*NEO PI-R*)	Before and after treatment in winter and during the summer months	SAD ↑ higher Neuroticism and Openness scores and ↓ Extraversion and Conscientiousness scores in summer compared to the norm data. SAD ↑ in Neuroticism, ↓in Extraversion, Openness, and Conscientiousness from summer to winter.
Gordon et al. 1999	SAD, n= 45	CS	Personality (*NEO PI-R*)	Summer (months not specified)	SAD ↑ Neuroticism compared to norm data.
Lingjaerde et al. 2001	SAD, n=82 Norwegian reference group, n=165	CS	Personality (5-PFs)	Summer	SAD ↑ scores on Emotional instability (corresponding to Neuroticism), Agreeableness and Sugency (corresponding to Extraversion) ↓ scores on Conscientiousness compared to norm data.

Notes: Abbreviations: Groups/sample size: HC= Healthy controls, MDD= Major Depression Disorder, SAD= Seasonal Affective Disorder. Design: CO = Cross Over, CS = Cross Sectional, CC = Case-Controlled study, PS = Prospective Study, DBPG = Double-Blind Parallel-Group, IS = Intervention Study. Outcome measures (*and instruments*): ASQ= Attributional Style Questionnaire, ATQ= Automatic thoughts questionnaires, DAS = Dysfunctional Attitudes Scale, CFQ = Cognitive Failures Questionnaire, DER = The Daily Emotion Records, NEO PI-R = NEO Personality Inventory – Revised, RSQ = Response Styles Questionnaire, PES = Pleasant Events Schedule, POMS = Profile of Mood States, SMTS = Simultaneous matching-to-sample test, DMTS = Delayed Matching-to-Sample tests, WRPAB = Walter Reed Performance Assessment Battery, 5-PFs = The Big Five Personality factors.

The following section will describe the aims and hypotheses of the three published studies included in this thesis.

AIMS AND HYPOTHESES

The overall aim of the three published studies included in this thesis was to examine trait-like and state-dependent characteristics in cognitive functions including non-emotional and emotional processing and self-perceived personality in individuals with SAD. We further aimed to examine whether cognition and personality characteristics in individuals with SAD were associated with depressive symptomatology. These aims were addressed by undertaking an extensive neuropsychological test battery, self-report questionnaires and psychiatric interviews in individuals diagnosed with SAD and compared with age-, sex and education-matched healthy controls in summer and in winter.

Aims and hypotheses of study 1

In study 1, we aimed to investigate seasonal changes in inhibitory control and identification of emotional facial expressions in individuals with SAD compared with healthy controls. Based on the SAD and MDD literature we tested the following hypotheses: (1) In winter, individuals with SAD will exhibit more failures to inhibit prepotent responses to negative emotional facial expressions, and display impaired identification of happy faces compared to healthy controls. (2) In summer, these affective cognitive biases would be comparable between individuals with SAD and healthy controls.

Aims and hypotheses of study 2

In study 2, we aimed to investigate seasonal changes in working memory, cognitive processing- and motor speed in individuals with SAD as compared to healthy controls. We also aimed to investigate whether any SAD-related impairments in working memory, partly arose from slowed cognitive processing speed. Finally, we aimed to investigate whether cognitive impairments were related to the seasonal change in depressive symptoms in SAD. Based on the existing SAD and MDD literature, we hypothesized that: (1) In winter, individuals with SAD will exhibit impairments in working memory compared to controls, whereas working memory performances in SAD normalizes in summer. (2) In winter and summer, individuals with SAD will exhibit impairments in cognitive processing- and motor speed compared to healthy controls.

Aims and hypotheses of study 3

In study 3, we aimed to examine the influence of Neuroticism on depression severity when assessed during the remitted phase. We also aimed to investigate group differences and group-by-season differences in FFM personality traits in individuals with SAD, compared to healthy controls. Based on the existing SAD literature, we tested the following hypotheses: (1) In individuals with SAD, higher scores on Neuroticism in the remitted phase are associated with more severe depressive symptoms in the symptomatic phase. (2) Individuals with SAD will exhibit higher scores on Neuroticism and Openness and lower scores on Extraversion, compared to controls in both summer and winter. (3) Individuals with SAD will differ in their personality trait scores in summer versus winter on the personality traits Neuroticism, Extraversion, Openness, and Conscientiousness whereas subject ratings remain stable.

METHODS

Four seasons fill the measure of the year; There are four seasons in the mind of man.

- John Keats (English romantic poet)

METHODS

Paper 1-3 are based on data from the same study. Details about the study methodology can be found in the three papers. The following sections, cover the recruitment procedure and description of participants and study design. The study was approved by the Danish Ethics Committee (H-1-2010-085 with amendments) and in line with the World Medical Association Declaration of Helsinki; prior to study participation, all participants signed informed consents after receiving oral, as well as written, information on the study.

Recruitment procedures

Volunteers were invited for a study on 'winter depression" using newspapers, the Internet, and bulletin boards at libraries. Volunteers who were interested in participating were then interviewed for evaluation of eligibility according to the following inclusion and exclusion criteria:

Inclusion criteria:

- Age between 18-45 years
- BMI < 25
- Non-smokers
- Normal medical and neurological examination
- Fluent in Danish
- Copenhagen residency

Exclusion criteria:

- Current or lifetime significant medical history, including neurologic or psychiatric (ICD-10) disorders
- Severe head trauma
- Pathological findings on medical or neurological examinations, blood tests or Magnetic Resonance Imaging (MRI) scans
- Current psychological or psychiatric treatment
- A family history of psychiatric disorders
- Retinal pathology
- Severe visual or hearing impairments
- Current use of medication which effects the 5-hydroxytryptamine (5-HT) system or with a photosensitizing effect
- Use of illegal drugs more than 10 times in lifetime. Cannabis was allowed up to 50 times in lifetime
- Alcohol abuse
- Travelling to countries with a sun ratio significantly different from Denmark 6 months prior to the test sessions
- Current or planed pregnancy
- Unstable circadian rhythm (e.g. Night shift work)

Additional exclusion criteria for eligible SAD volunteers:

- Use of psychological or psychotropic drug treatment, including BLT within the last year.

Additional exclusion criteria for eligible healthy volunteers:

- If included in the study: Major Depression Inventory (MDI) score > 21, indicating depressed mood, in summer or winter

Volunteers who met the initial screening criteria further completed a Danish version of the Seasonal Pattern Affective Questionnaire (SPAQ) (Rosenthal et al., 1984). SPAQ is a self-administered screening instrument for SAD and examines seasonal variations with six items; sleep, social activity, appetite, mood, body weight and energy. The SPAQ Global Seasonality Score (GSS), which indexes the degree of seasonality symptoms, is obtained by summing the scores of the six items (GSS range from 0 to 24). Potential SAD candidates were required to have a GSS≥11 and rate seasonality to be at least a 'moderate' problem. Potential healthy controls were required to have a GSS≤10 and rate no problems with seasonality symptoms (Kasper et al., 1989).

Psychiatric assessment

Eligible SAD candidates were interviewed by two psychiatrists in summer and in winter. To establish the presence of a SAD diagnosis, International Classification of Diseases, 10th revision (ICD-10) was used to confirm a major depression (WHO, 2005) and the SAD criteria formulated by Rosenthal et al. (1984) were used to confirm a seasonal pattern of depressive episodes. To exclude psychiatric co-morbidity, Schedules for Clinical Assessment in Neuropsychiatry (SCAN V2.1) (Wing et al., 1999) was used. Finally, the Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder version (SIGH-SAD) (Williams, 1988), was used to index the severity of SAD depressive symptoms. Individuals with SAD who presented with psychiatric co-morbidity (axis I and axis II disorders), failed to spontaneous remit in summer, or failed to develop a depressive episode in winter the following season after inclusion, were excluded. As a result of the initial screening procedure, 44 SAD candidates were referred to a psychiatric assessment. Thirteen of these candidates were excluded because of co-morbidity or failure to fulfil the SAD diagnostic criteria. Three participants (two individuals with SAD and one healthy control) dropped out of the study between the summer and winter psychological test sessions

Participants

The final study included a group of 29 individuals meeting the SAD diagnostic criteria and a healthy control group of 30 healthy controls, matching the individuals with SAD on age, sex and education.

Educational scores were rated on a 5-point Likert scale from 1 (no vocational education) to 5 (academic education > 4 years). Detailed characteristic of the study sample can be found in the papers covering study 1-3.

Study design

In this longitudinal case-control study, all participants completed a neuropsychological test battery, mood and personality questionnaires one time in the summer month i.e., May-July and once in the winter months i.e., November-January. The interval between psychological assessments was 4.5–6.0 months (Figure 3). Within all test sessions, the order of neuropsychological tests was the same. For healthy controls, IQ was examined at the first cognitive test session, whereas IQ for individuals with SAD were examined during remission. To account for the confound of seasonal effects with practice effects, half of the participants in each group were tested first in winter and then in summer, while the other half was tested in the reverse seasonal order.

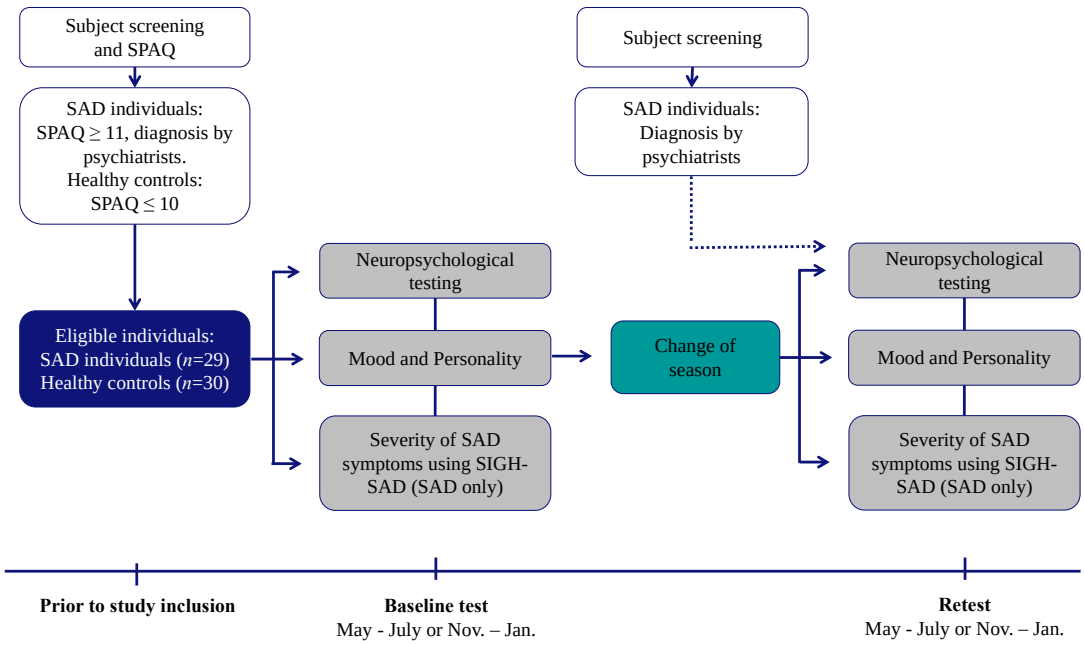

Figure 3. Study design. *Notes:* The figure shows an overview of the study design and points in time for the psychiatric and psychological assessments. Only the individuals with SAD were referred to psychiatric evaluation.

The following sections cover the IQ test, the cognitive tests and the self-report questionnaires used in the three studies. Study 1 applied the Emotional Go/NoGo task and the Emotional Face Identification task (EFIT). Study 2 applied the Letter-Number Sequencing task (LNS), the Symbol Digit Modalities Test (SDMT) and the Simple Reaction Time (SRT). Study 3 applied the NEO Personality Inventory-Revised and the Major Depression Inventory (MDI).

The Reynolds Intellectual Screening Test (RIST)

The RIST measures IQ. It is a verbally administered test of approximately 20 minutes and includes a verbal ("Guess what") and a non-verbal ("What does not fit") subtest from the Reynolds Intellectual Assessment Scales (RIAS). The index is available in a normed Danish version and has been developed for scientific purposes (Reynolds and Kamphaus, 2003). The main outcome is the RIST index, a measure of the overall age-adjusted IQ.

Hot cognitive tests

The Emotional Go/NoGo Task

The emotional Go/NoGo task measures the ability to inhibit prepotent responses for non-emotional and emotional stimuli. It is a computerized test of approximately 20 minutes and includes one emotional subtask comprising emotional faces and two non-emotional control subtasks comprising either geometric figures or neutral female and male faces. Participants are instructed to respond to a target (go stimuli) as rapidly and accurately as possible and to withhold the response to a distractor (nogo stimuli). The ratio of target to distractor stimuli is 75% to 25% respectively and the stimuli are displayed for 500 milliseconds (ms) followed by an inter-stimulus interval (ISI) of 700 ms displaying a fixation cross. The first subtask consists of four randomized blocks of geometrical figures (i.e., tilted squares as go, and squares as nogo stimuli, and vice versa), with two blocks presented in the beginning and two in the end of the overall task (see Figure 4, A). The second subtask consists of eight randomized blocks of fearful, happy, angry, sad or neutral faces. Within each emotional block, an emotional face was always paired with a neutral face (i.e. if an emotional facial expression served as go stimuli a neutral face served as nogo stimuli, and vice versa (see Figure 4, B). The last subtask consists of two randomized blocks of neutral male and female faces (i.e. female faces as go stimuli and male faces as nogo stimuli, and vice versa), presented before the last two blocks of geometric figures (see Figure 4, C). Our main outcome was false alarms (responses on a nogo trial, reported as % correct nogo trials). Impaired inhibitory control of negative stimuli, were calculated as mean false alarms for conditions with negative (fearful, angry and sad) nogo trials. Impaired inhibitory control of neutral stimuli, were calculated as mean false alarms for conditions with neutral faces nogo trials.

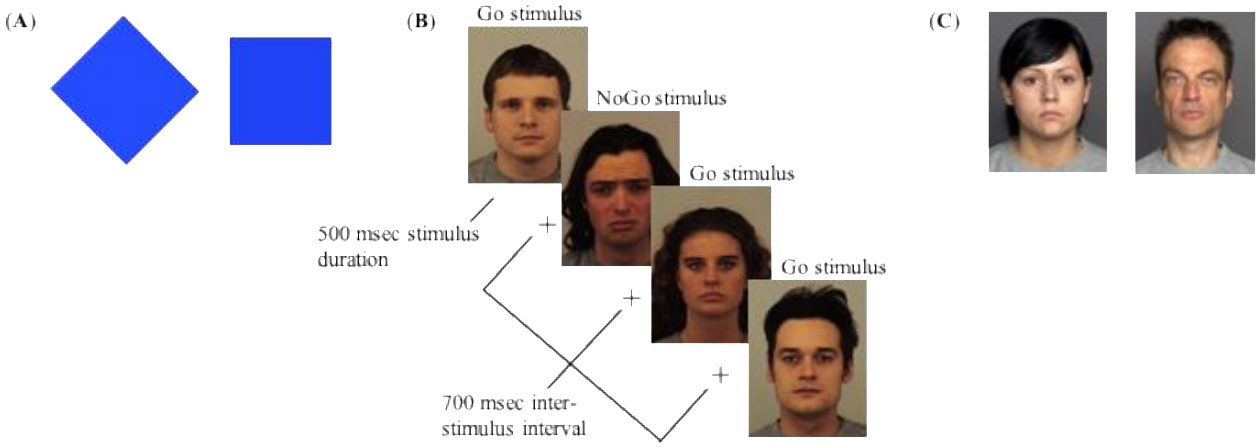

Figure 4. Illustration of the Emotional Go/NoGo Task. *Notes:* (A) The geometric figures used in the non-emotional control subtask. (B) An example of an emotional block where neutral faces served as go stimuli and sad faces served as nogo stimuli (Face image ID: AM31NES, AM01SAS, AF08NES, AM06NES selected from the Karolinska Directed Emotional Faces series (Lundqvist and Litton, 1998)). (C) An example of a neutral female and male face used in the non-emotional control subtask.

The Emotional Identification Task (EFIT)

The EFIT measures the ability to correctly identify emotional facial expressions of happiness, sadness, anger, disgust and fear at different intensities. It is a computerized test of approximately 15 minutes. Each of the facial expressions were morphed with the neutral face image of the same face identity producing emotional resolutions of 0% (100% neutral) 20%, 30%, 40%, 50%, 60%, 70%, 80% and 100% emotional valence (see Figure 5, A). The task included the presentation of 172 face image in total. A face image was displayed on the top of a black screen with a hexagon made of six circles including the words for each of the five facial expressions or neutral shown below (see Figure 5, B). Participants are orally instructed to label the emotional or neutral expression by moving a cursor to the circle of choice, as quickly and accurate as possible. The arrangement of the circles in the hexagon were randomly distributed between task sessions, however, the circles were stationary within a task session in order to habituate the participant to the location of the circles. Accuracy in identifying emotional facial expressions, reported as d-prime (d') was our main outcome. d' is a sensitivity index of accuracy accounting for response bias, and higher d' values signify better detectability to the presence of emotional facial expressions.

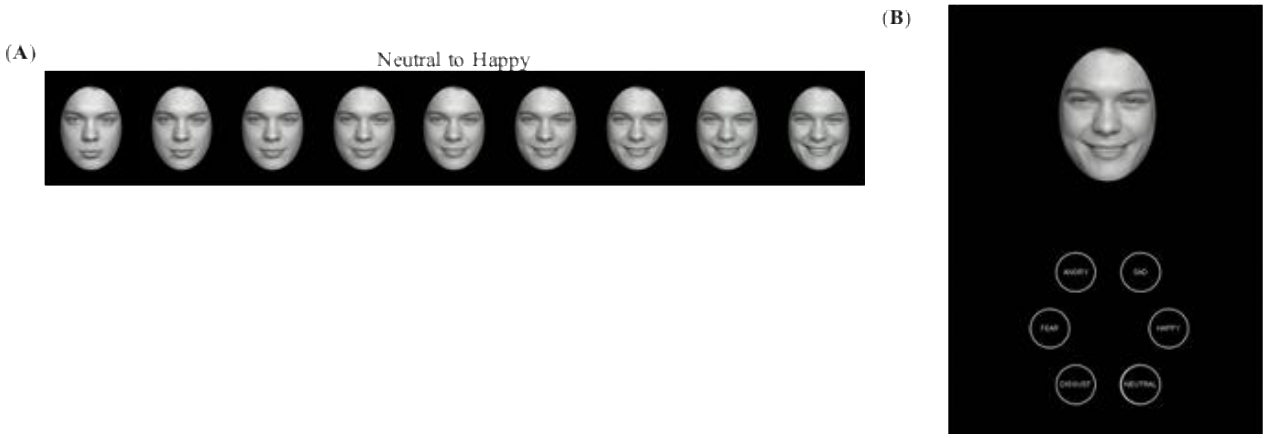

Figure 5*:* Illustration of the Emotional Face Identification Task. *Notes:* (A) The morphing of a neutral facial expression with a happy facial expression. To the left is shown a 100% neutral image and to the right is shown a 100% happy face image, with the different resolutions displayed between the two original images. (B) Example of identification of a happy facial expression.

Cold cognitive tests

Letter-Number Sequencing (LNS)

The LNS measures working memory capacity and is a subtest from the Wechsler Adult Intelligence Scale-III (Wechsler, 1997). LNS is an auditory verbal test of approximately 10 to 15 minutes, in which the tester orally reads a series of letters and numbers with increasing difficulty, with two to eight items per series (e.g. E-1-R-8-M-7). The participants are instructed to recite the numbers in ascending order followed by the letters in alphabetical order (e.g. 1-7-8-E-M-R). Our main outcome was total number of correctly recited series. LNS scores ranged from 0-21.

Symbol Digit Modality Task (SDMT)

The SDMT (Smith, 1982) measures cognitive processing speed and working memory capacity (Salthouse, 1992). The SDMT is a validated paper-and-pencil test of approximately 3 to 4 minutes, in which participants examine a reference key matching nine abstract symbols with the digits from 1-9. The participant has 90 seconds to translate as many symbols as possible. Our main outcome was the total number of correctly translated symbols. SDMT scores ranged from 0-110.

The Simple Reaction Time Task (SRT)

The SRT measures motor speed and is a test from the Cambridge Neuropsychological Test Automated Battery (CANTAB). It is a computerized test of approximately 6 to 10 minutes, in which the participants are presented with a white square on the screen with a variable interval, and are

instructed to press a keyboard button as quickly and correctly as possible when they see the white square. Our main outcome, was mean reaction time latency (ms).

NEO Personality Inventory – Revised (NEO PI-R)

The NEO PI-R (Costa and McCrae, 1992) is a self-report questionnaire that measures the FFM personality traits: Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness and the six sub-facets that define each trait (see Table 1), and has been normed for Danish use (Skovdahl et al., 2011). Each of the 240 items of NEO PI-R consists of a statement to which the participants rate their level of agreement (0 = strongly disagree, 4 = strongly agree) on a 5-point Likert scale. Example of items from the Neuroticism scale: "I often get angry at the way people treat me" or "I am not a worrier". NEO PI-R trait scores ranged from 0-192, and NEO PI-R sub-facets scores range from 0-32.

The Major Depression Inventory (MDI)

The MDI (Bech et al., 2001) is a self-rating inventory developed to measure depressive symptoms according to DSM-IV and ICD-10 diagnostic criteria. It comprises 10 items (e.g. "Have you felt a lack in energy and strength?" or "Have you had difficulty in concentrating, e.g. when reading the newspaper or watching television?"), and participants rate how often depressive symptoms had been present over the past two weeks (0 = at no time, 5 = all the time). MDI scores ranged from 0-50.

Statistics

For all three studies, demographic and clinical data were analysed with univariate analysis of variance (ANOVAs) or Mann–Whitney U tests for continuous data and χ^2 or Fisher's Exact test for categorical data. Seasonal difference in clinical data was analysed with Wilcoxon signed-rank tests. In all three studies, seasonal test order, sex, age and IQ (and BMI for study 3 only) were included as covariates in linear regression models and linear mixed effect models. Tests of significance was applied across all three studies. Maximum likelihood ratio tests were used in study 2 and log-likelihood ratio tests or Wald tests were used in study 3. Statistical analyses were conducted in SPSS (v24.0) and R (v3.3.0) (R Core Team, 2016), with alpha level of 0.05 (two-tailed).

In study 1, group comparisons in inhibitory control and identification of emotional facial expressions in winter and summer respectively were evaluated with multiple linear regression models. For significant group differences in inhibitory control of negative faces and identification of happy faces, follow-up analyses for each of the emotional faces were carried out. For significant follow-up

analyses, within-group changes from summer to winter were examined using paired t-tests. P-values in analyses of inhibition of negative faces and identification of happy faces in summer and winter were corrected for conducting four tests, using the Bonferroni-Holm multiple comparison procedure (Holm, 1979). Other p-values were reported unadjusted.

In study 2, group-by-season effects and main effects of group and season on LNS, SDMT and SRT were assessed with linear mixed effect models with a random intercept for each individual. In significant interaction and/or main effects of group on LNS, we evaluated whether working memory deficits arose from differences in cognitive processing speed by correcting the LNS model for SDMT performance and covariates. In significant interaction and/or main effects of group on SDMT, we further evaluated whether a slowing in cognitive processing speed arose from differences in motor speed by correcting the SDMT model for SRT performance and covariates. Finally, in individuals with SAD, significant interaction and/or main effects of group on LNS, SDMT and SRT, were examined in relation to change in severity of depressive symptoms, as defined by absolute ΔSIGHSAD = winter score – summer score.

In study 3, association between Neuroticism scores during remitted state and MDI scores during the depressed state in individuals with SAD were evaluated in a linear regression model. Group-by-season effects and main effects of group and season on the FFM trait in question were evaluated with linear mixed effect models. When group or group-by-season effects were significant, a linear mixed model was fitted on each of the sub-facets of the trait. P-values resulting from analyses on FFM traits and sub-facets were corrected for conducting five and six tests respectively, using the Bonferroni-Holm multiple comparison procedure (Holm, 1979). Other p-values were reported unadjusted.

RESULTS

...it is chiefly the changes of the season which produce disease, and in the seasons the great change from cold or heat.

- Hippocrates

RESULTS

In the following section, the main study findings are summarized. Other results, tables and explanatory text are presented in detail in the papers covering study 1-3.

Study 1

In this study, on the Emotional Go/NoGo task, we found that compared to controls individuals with SAD made more false alarms when inhibiting responses to negative faces (p=0.033) only during the depressive phase. This group difference was driven by angry (p<0.001) and sad faces (p=0.011) (see Figure 6). False alarms for fearful, happy and neutral faces and geometric figures were not different in the two groups in summer or winter. From summer to winter, individuals with SAD increased in false alarms for angry faces (p=0.038), whereas healthy controls decreased in false alarms for angry faces (p=0.020). In the EFIT, individuals with SAD displayed reduced identification of happy faces (p=0.032) in their depressive phase compared with healthy controls. No seasonal differences in identification of happy faces were observed within the two groups. Identification of negative faces were not different in the two groups in summer or winter.

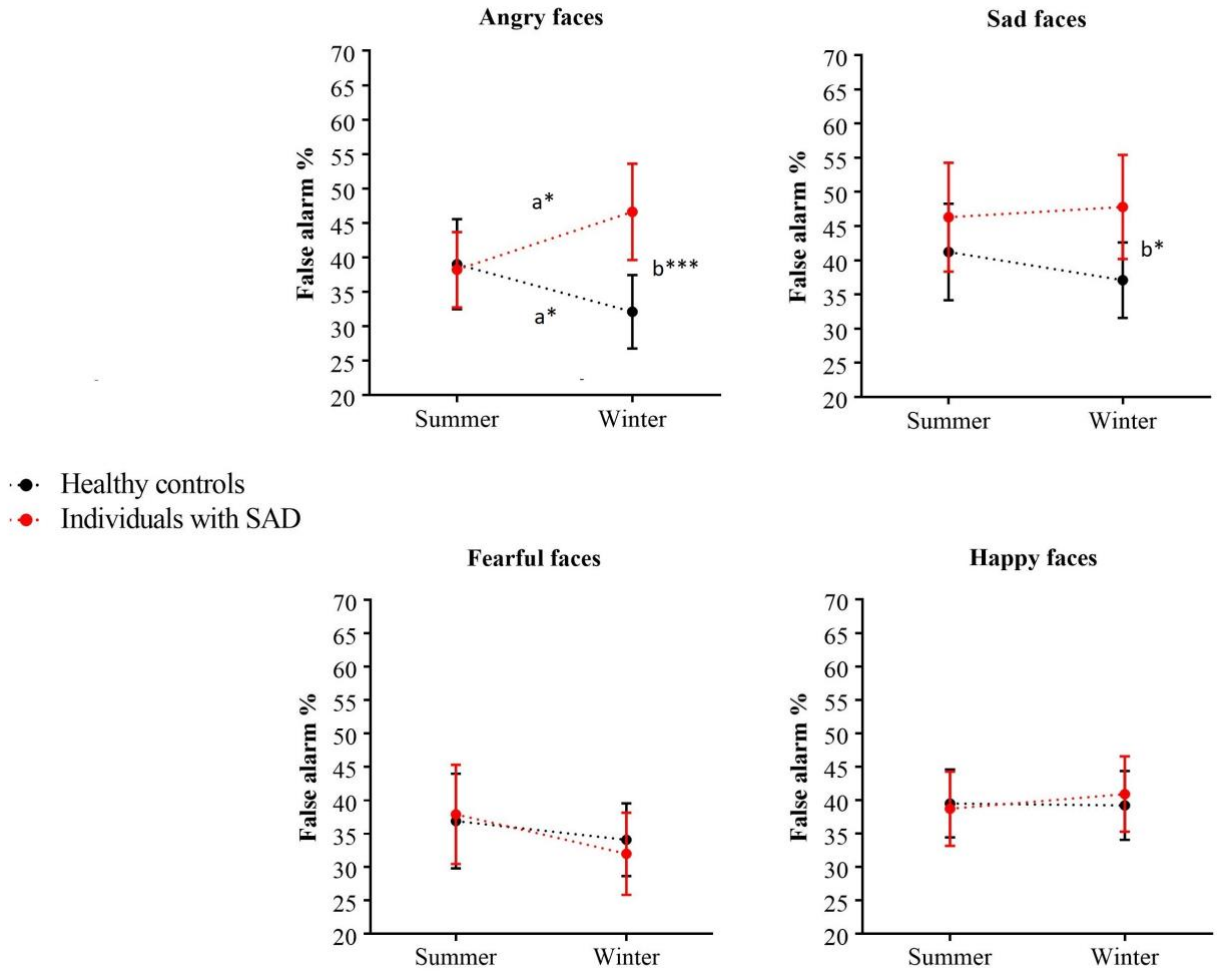

Figure 6. Inhibitory control of emotional faces. *Notes:* The figure shows inhibition performance on angry, sad, fearful and happy faces in summer and winter for individuals with Seasonal Affective Disorder (SAD) and controls. The graphs represent mean false alarms in percentage and error bars indicate standard deviations. a* Within-group changes from summer to winter, $p<0.05$. b* Group differences in winter, $p<0.05$. b*** Group differences in winter, $p<0.001$.

Study 2

In this study, we found that both during the remitted phase in summer and during the depressive phase in winter, individuals with SAD recited fewer correct series of letters and numbers on the LNS, translated fewer correct symbols on the SDMT and presented with higher average response times on the SRT compared to healthy controls (see Figure 7). We did not find any group-by-season effects on LNS, SDMT or SRT, p-values$\geq$0.458.

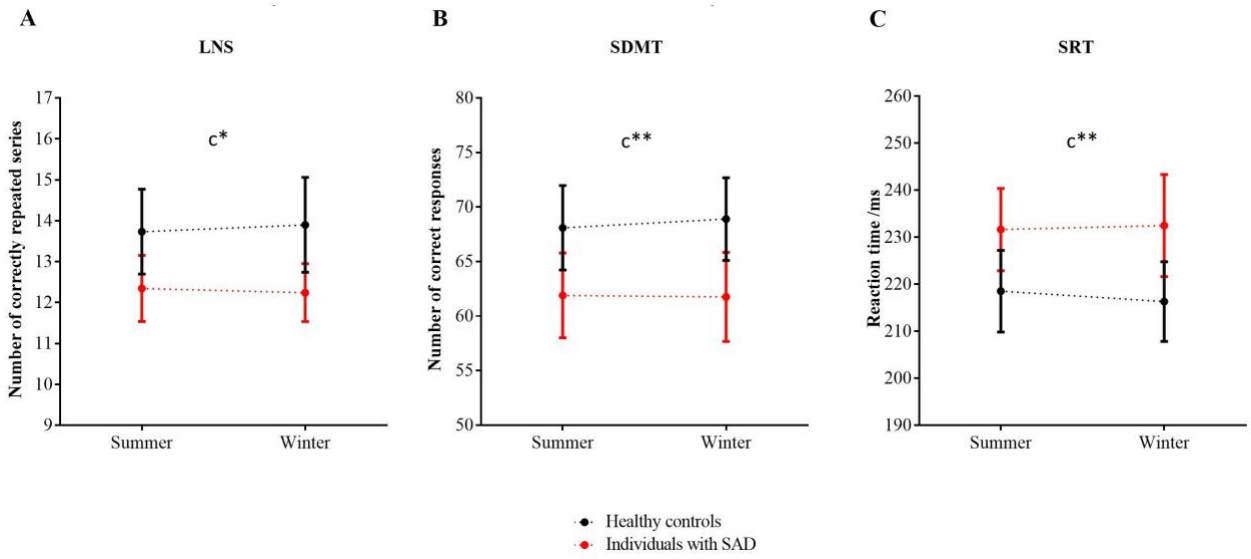

Figure 7. Performance on cold cognitive tests. *Notes:* The figure show scores on: Letter-Number Sequencing (LNS) (A), the Symbol Digit Modality Task (SDMT) (B), and the Simple Reaction Time (SRT) (C) in summer and in winter for individuals with Seasonal Affective Disorder (SAD) and healthy controls. The graphs represent mean raw scores and error bars indicate standard deviations.

When we adjusted the LNS model for performance on the SDMT, the significant group effect on LNS was no longer present (p=0.125) and SDMT significantly accounted for the SAD-related working memory deficits (p=0.001). These results imply that much of the higher-order working memory impairments seen in individuals with SAD, emerged from slowed lower-order cognitive speed processes. In addition, when we adjusted the SDMT model for performance on the SRT, the significant effect of group on SDMT was still present (p=0.013), suggesting that the SAD-related slowing in cognitive processing speed, was not explained by slowed motor processes.

When we investigated the association between LNS, SDMT and SRT and seasonal change in SIGH-SAD scores in the SAD group, we found that SDMT scores were negatively associated with change in SIGH-SAD scores (p<0.001), suggesting that slowed cognitive processing speed independent of season were associated with a higher change in SAD depressive symptoms from summer to winter (see Figure 8). We did not observe associations between LNS or SRT and change in SIGH-SAD scores, p-values≥0.352.

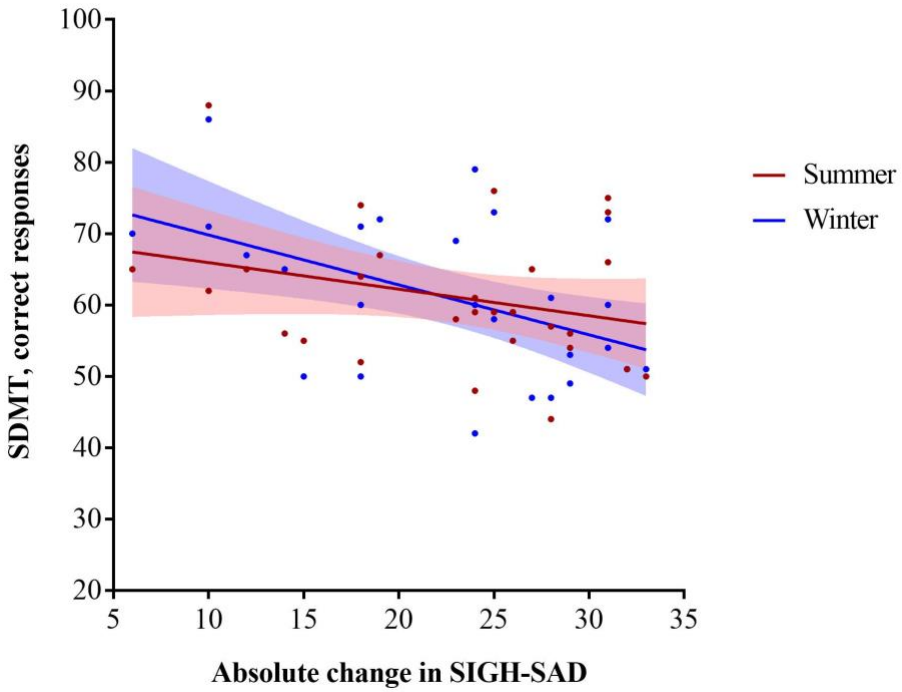

Figure 8. Associations between cognitive processing speed in summer and winter and seasonal change in depressive symptoms. *Notes:* The figure shows a scatter plot of the negative correlations between raw scores on the Symbol Digit Modality Task (SDMT) in summer (red line) and in winter (blue line) plotted against the seasonal change in the Structured Interview Guide for the Hamilton Rating Scale for Depression—Seasonal Affective Disorder version (SIGH-SAD) scores in the Seasonal Affective Disorder (SAD) group (p<0.001). Values are raw scores and shadings for each line represent 95% confidence intervals.

Study 3

In this study, we found that in the SAD group, Neuroticism scores during remission were positively associated with MDI scores during the depressed state (p=0.04) (see Figure 9). Importantly, this association was not evident in the healthy control group (p=0.171).

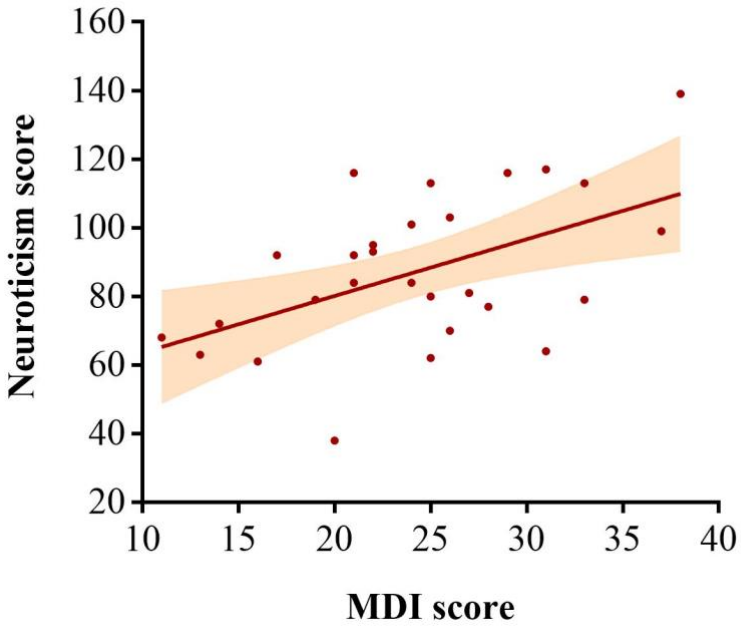

Figure 9. Association between Neuroticism in summer and depressive symptoms in winter in the SAD group. *Notes:* The figure shows a scatter plot of the positive correlations between Neuroticism raw scores in summer, plotted against scores obtained from the Major Depression Inventory (MDI), and scores during the depressive phase in individuals with Seasonal Affective disorder (SAD) ($p<0.04$). Values are raw score and shading for the red line represent 95% confidence intervals.

When investigating self-perceived personality characteristics in individuals with SAD compared to healthy controls, we found that during the depressive phase, individuals with SAD presented with higher levels of trait Neuroticism ($p=0.002$) and higher levels of the Neuroticism sub-facets of Anxiety ($p=0.035$), Angry hostility ($p=0.002$), Depression ($p<0.001$) and Vulnerability ($p=0.010$). Notably, the two groups presented with similar levels of Neuroticism during the remitted phase. A group-by-season effect was observed for trait Neuroticism ($p=0.033$), and for the Neuroticism sub-facets of Angry hostility ($p=0.043$), Depression ($p=0.001$) and Vulnerability ($p=0.014$), where individuals with SAD showed a larger change from summer to winter, compared to healthy controls (see Figure 10). The group-by-season effects emerged primarily because individuals with SAD significantly increased in Neuroticism from summer to winter, whereas the Neuroticism scores of healthy controls did not change over the season.

Moreover, we found that during the depressive phase, individuals with SAD presented with lower levels of Extraversion ($p=0.019$) and lower levels of the Extraversion sub-facets of Warmth ($p=0.023$) and Positive emotions ($p=0.003$). The groups presented with similar levels of Extraversion during the remitted phase. A group-by-season effect were also observed for Extraversion ($p=0.007$) (see Figure

10) and for the Extraversion sub-facet Positive emotions (p=0.004), where individuals with SAD showed a larger change from summer to winter compared to healthy controls. The group-by-season effect emerged primarily because individuals with SAD significantly decreased in Extraversion from summer to winter, whereas the Extraversion scores of healthy controls did not change over the season.

For the traits Openness, Agreeableness and Conscientiousness, we did not find any effect of group in summer or winter, season or group-by-season.

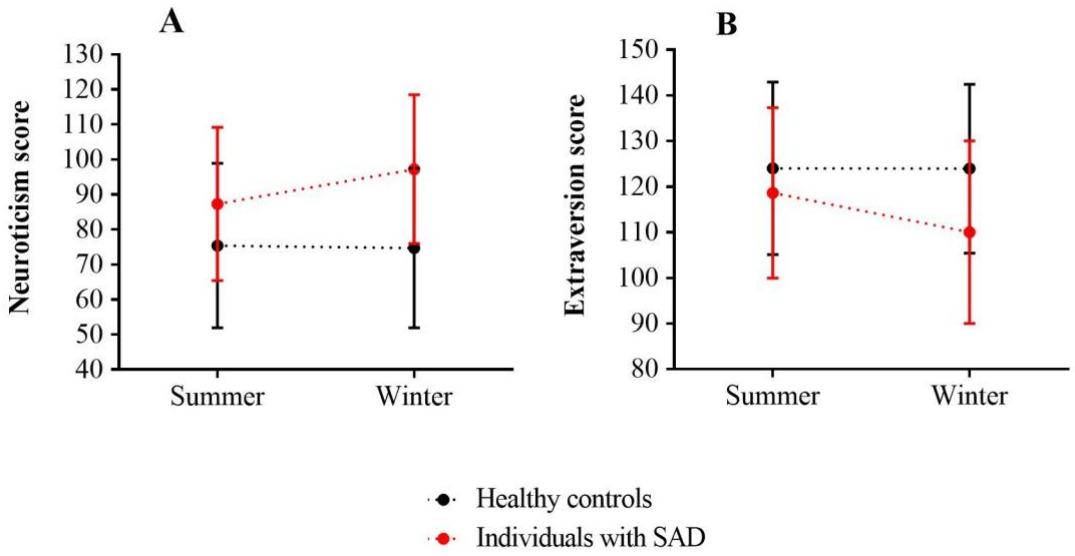

Figure 10. Seasonal changes in Neuroticism and Extraversion scores. *Notes:* The figure shows mean Neuroticism scores (A) and mean Extraversion scores (B) in summer and in winter for the Seasonal Affective Disorder (SAD) and healthy control group. The graphs represent mean raw scores and error bars indicate standard deviations.

Cross-study analyses (not included in the papers)

Association between inhibitory control and working memory

It is not clear whether working memory and inhibitory control are separate cognitive functions or are dependent of one another. For example, inhibitory control may support working memory performance, by keeping irrelevant information out of working memory. Conversely, inhibitory control may be a behavioural product of working memory in the sense that holding information firmly enough in working memory may allow individuals to act appropriately (Diamond, 2013). If these cognitive functions are dependent of one another, it is relevant to examine whether our observed impairments in inhibition of angry and sad faces can be accounted for by working memory deficits. Based on our findings in study 2 where we showed that cognitive processing speed significantly

accounted for the SAD-related working memory deficits, it may also be relevant to control for SDMT performance in analyses addressing inhibitory control functioning. Therefore, in post-hoc cross-study analyses, we examined whether winter-related impairments in inhibition of angry and sad faces respectively arose from working memory impairments and/or reduced cognitive processing speed.

We conducted two linear regression models, using the false alarm winter scores for angry and sad faces respectively, as dependent variables and group as predictor variable, while adjusting for LNS and SDMT summer and winter scores, test-order, age, sex and IQ. This allowed us to evaluate direct effects of SAD on inhibitory control of angry and sad faces, after controlling for the effect of differences in working memory and cognitive processing speed in summer and in winter. When adjusting the two inhibition models for LNS and SDMT performance, the group effect on inhibition of angry in winter remained significant ($t(49)=-2.98$, $p_{unadjusted}=0.004$, $r_p=0.39$, 95%CI [-23.26, -4.54]) whereas the group effect on inhibition of sad faces in winter was no longer significant ($t(49)=-1.52$, $p_{unadjusted}=0.135$, $r_p=-0.21$, 95%CI[-17.23, 2.38]). In both inhibition models neither LNS nor SDMT scores significantly accounted for the inhibitory control performance p-values$\geq$0.135 (unadjusted). These results suggest that performance on the Emotional Go/NoGo task do not seem to be dependent on performance on LNS and SDMT in our study participants.

DISCUSSION

…Black pile…when it is overheated…produces cheerfulness accompanied by song and frenzy…if it be cold beyond due measure, it produces groundless despondency; hence suicide by handing occurs.

- Aristotle

DISCUSSION

The present thesis aimed to investigate depression-related cognition and personality characteristics longitudinally, based on a naturalistic depression model, specifically the seasonal changes in depressed status in individuals with SAD. In particular, an attempt was made to disentangle trait-like from state-dependent markers within cognition and personality in SAD to get a better understanding of the possible vulnerability markers involved in SAD.

The reader is referred to papers, 1, 2, and 3 for a detailed discussion of the study findings, implications and comparison with existing literature. In the following, a discussion of the main findings is summarized.

Trait-like and state-dependent markers of SAD

In all three studies, we aimed to disentangle trait-like markers from transient state markers in inhibitory control, emotional face identification, working memory, cognitive processing, motor speed and personality in individuals diagnosed with SAD, compared to demographically matched healthy controls. We found that individuals diagnosed with SAD, failed to inhibit prepotent responses to angry and sad faces, and to identify happy facial expressions (study 1), and had higher levels of Neuroticism and lower levels of Extraversion (study 3) in the symptomatic phase, but not in the remitted phase compared to healthy controls. These results suggest that individuals with SAD display state-dependent processing bias towards negative information but also away from positive information in the depressive state only. Our results further imply that inhibitory control, emotional face identification, Neuroticism and Extraversion may be sensitive markers of SAD psychopathology. In study 2, we found that individuals with SAD showed a season-independent pattern of impairments in working memory, cognitive processing and motor speed, suggesting that these cognitive impairments may constitute trait-like markers of SAD.

One possible interpretation across these findings on cognition, is that certain hot cognitive functions such as inhibition of negative stimuli, emotional face identification appear to constitute state-dependent features of SAD, whereas certain cold cognitive functions such as working memory, cognitive processing speed and motor speed, appear more trait-like. If this interpretation holds true, how can this be explained? This question is difficult to answer and was not the aim of our study. It has been suggested that prefrontal and hippocampal abnormalities may impair top-down processes related to cold cognition (e.g. executive functions, attention, memory and cognitive processing).

Impaired top-down processes, in combination with increased activation of amygdala in response to stress, have also been suggested to increase negative biases in hot cognitive processes (e.g. rumination) (Buthmann et al., 2016, pp. 5-6). It could be speculated that individuals with an increased vulnerability profile to SAD cannot exert efficient top-down control over hot cognitive processing. This combined with increased amygdala activation, as a result of facing the stress of winter, could explain why we "only" observe impaired inhibition of angry and sad faces and identification of happy during the symptomatic phase, and observe season independent impairments in working memory and cognitive processing. Supporting the notion that hot and cold cognitive functions may be differently affected by SAD, is a recent study using the same cohort as presented in this thesis and study design. Here we investigated recall of affective and non-affective words within working memory, using the Verbal Affective Memory Test-24 (VAMT-24) (Jensen et al., 2015). We showed, that while memory of positive words decreased significantly more from summer to winter in SAD compared to healthy controls, recall of neutral words did not. However, individuals with SAD recalled less neutral words in summer and in winter compared to controls, at a statistical trend level (p=0.061 and p=0.062). Combined, these findings support the existence of separate cognitive processes for hot and cold stimuli in SAD. Yet, it is also possible that the difference in memory for certain types of valenced material can be attributed to the differential sensory modalities that VAMT-24 and LNS tasks rely on; VAMT-24 is a visual memory test whereas LNS is an auditory memory test and auditory tests seem to be more mentally fatiguing for participants compared to visual memory tests (Hamada, 1990).

While our longitudinal study is a powerful design for separating state-related cognitive impairments that co-exist with the depressive symptoms from trait-like cognitive markers, it is not possible on the basis of our data, to examine whether or not the observed impairments in cold cognition precede SAD, and thereby represents traits or scars. In order to examine this, longitudinal study designs are needed in which the cognitive functions of interest are assessed in participants prior to the first SAD depressive episode, at a later point in time of the SAD diagnosis and during remission from the SAD depressive episode. Such a study design can establish both the temporal precedence of the cognitive functions and the independence of symptoms, but also avoid confounding effects of previous SAD depressive episodes, treatment and hospitalization on cognition (Riskind and Alloy, 2005). Given the short time period between depression and remission in SAD, and that state-dependent cognitive impairments often disappear gradually and simultaneously with the decrease of residual affective symptoms, it is also possible, that the observed season-independent cold cognitive impairments require more time to completely disappear compared to the seasonal occurring affective symptoms, thus reflecting actual cognitive state-markers of SAD. Regardless of whether these cognitive

impairments represent traits or scars of SAD, these residual cognitive symptoms are present after the improvement of affective symptoms, and may affect functional recovery and impact on the quality of life and every-day functioning (Jaeger et al., 2006; Rock et al., 2014).

Clinical importance of the cold cognitive impairments in SAD?

We reported statistically significant group differences on LNS, SDMT and SRT in summer and in winter (study 2), but on average individuals with SAD and healthy controls only differed with a 'few' correct responses or ms on the LNS, SDMT and SRT. This raises the question: To what extent are individuals with SAD cognitively impaired compared to their non-SAD counterpart? And does this have an impact on their daily-life and professional functioning? Whether these cognitive dysfunctions fall within an impaired range or are clinically meaningful, is very difficult to answer reliably and falls outside the scope of our study. The lack of knowledge regarding the possible impact that cognitive impairment has on daily life functioning in individuals with non-seasonal depression has also been emphasized in the a review by Hammar and Ardal (2009). Some studies have classified cognitive impairments as performance that is 1.0 (Maruff and Jaeger, 2016) or 1.5 (Mackin et al., 2016) standard deviations (SD) below or above that of healthy controls. When applying these criteria, individuals with SAD in our study score within a clinically impaired range on all three tests on cold cognition (Table 3).

Table 3: Cold cognitive impairment associated with Seasonal Affective Disorder

	Cognitive test	Individuals with SAD	Healthy controls
Summer	LNS	12.4 ± 0.4	13.7 ± 0.5
	SDMT	61.9 ± 1.9	68.1 ± 1.9
	SRT	231.6 ± 4.3	218.5 ± 4.3
Winter	LNS	12.2 ± 0.4	13.9 ± 0.6
	SDMT	61.4 ± 2.0	68.3 ± 1.9
	SRT	232.5 ± 5.3	216.3 ± 4.1

Notes: LNS: Letter-Number Sequencing, outcome is total raw scores; SDMT: Symbol Digit Modalities Test, outcome is total raw scores; SRT: Simple Reaction Time, outcome is mean latency response (milliseconds). Data is shown as mean ± SD.

Meta-analyses show that the magnitude of cognitive impairments in MDD are low (Lee et al.; McDermott and Ebmeier, 2009), and cross-study analyses indicate that cognitive impairments are substantially greater in individuals with other illnesses such as chronic schizophrenia and Alzheimer's

Disease (AD) compared to MDD (Maruff and Jaeger, 2016, pp. 17, Figure 2.1). Based on these results, why have individuals suffering from depression and clinicians agreed that cognitive impairments in MDD are of clinical importance? One possible reason for this, as suggested by Maruff and Jaeger (2016, p. 16), relate to the degree of social engagement across the three patient groups; ~80% of the individuals with MDD are in full or part time education or employment, as compared to ~20% of the individuals with chronic schizophrenia and 0% of the individuals with AD (Maruff and Jaeger, 2016, pp. 18, Figure 2.2). Although comparing MDD to AD and chronic schizophrenia may be difficult, as AD and chronic schizophrenia are two more severe and chronic illnesses, these abovementioned results, could infer that individuals with severe cognitive impairments generally do not work, whereas most individuals with MDD continue to work or study. As discussed by Maruff and Jaeger (2016, p. 16), this is relevant, as it has been shown that even small declines in cognitive functioning is disruptive for daily activities in healthy individuals with part or fulltime jobs. For example, in most developing countries, it is discouraged or illegal to operate machinery when sleep deprived or affected by low levels of alcohol because it puts others at risk of danger. Interestingly, individuals with MDD are found to exhibit the same magnitude of cognitive dysfunctions as seen in individuals that are under the influence of low levels of alcohol (blood alcohol percent of 0.05) and individuals, who have been sleep deprived for 24 hours (Maruff and Jaeger, 2016, pp. 19, Figure 2.3), underlining that participation in work or education necessitate optimal cognitive functioning. To the best of my knowledge, similar comparative cross-study analyses have not included studies on SAD, but assuming that cognitive impairments, and employment numbers are higher or comparable between SAD and MDD, this raises the possibility that even a small magnitude of cognitive impairment could have a negative impact on daily-life and professional functioning for individuals with SAD.

Cognitive change at the level of the individual

Knowledge about the clinical importance of cognitive impairments in groups of individuals with SAD is relevant for the overall understanding of the level of cognitive dysfunction in SAD populations, however it cannot inform about change in cognitive dysfunction at the level of the individual, which is important in treatment settings. For example, an individual with SAD with a higher than mean level of cognitive functioning before the depressive episode, could exhibit a pronounced deterioration in cognition after the depression, but when compared to the mean cognitive performance level of a healthy control group, the degree of impairment falls within the "normal" limits, and may not be considered clinically important. Thus, comparing cognitive functioning in SAD with the mean of

healthy controls may underestimate the level of cognitive impairments in some of the individuals with SAD (as argued by Maruff and Jaeger (2016, p. 24).

If we acknowledge that the cognitive impairments associated with SAD are clinically important, researchers should seek to validate methods capable of tracking cognitive change on the individual level, in ways that could help clinical decision-making. Determining whether the premorbid levels of cognition for some individuals show a substantial and clinically important decline with the first depressive episode, would require longitudinal studies which examines the cognitive performance in individuals prior to, and after, a SAD diagnosis.

Vulnerability to SAD

Cognitive processing speed as a vulnerability to SAD

Vulnerability traits are typically perceived as a latent process, since they are not easily recognized (Ingram and Luxton, 2005, p. 35). Different approaches have been used to identify such latent processes, which often operate under the assumption that vulnerability traits are causally linked to the appearance of psychiatric symptoms (Ingram et al., 2011, p. 31). In study 1, we observed that the SAD-related slowing in cognitive processing speed independent of season were associated with the seasonal change in depressive severity, suggesting that a slowing in cognitive processing speed, act as a vulnerability to SAD. However, from a scar perspective, it could also be argued that the SAD-related slowing in cognitive processing speed represent an 'acquired vulnerability' developed as a consequence of the first SAD depressive episode(s), that subsequently influence on the development of depressive symptoms. Unfortunately, our data do not allow us to conclude that a slowing in cognitive processing precedes SAD or is causally (or prospectively) related to symptom development, and thus whether it represents a vulnerability trait of SAD. To study 'symptom development', study participants would have needed to be assessed in a fixed order (summer first, then winter) to have the necessary temporal course to give information about symptom development (from remission into depression). For about half of the participants, the winter assessment occurred first. Nonetheless, using a non-counterbalanced study-design may very likely have introduced a practice effect; i.e., improvements in cognitive test performance in winter, and thereby increased the likelihood of misinterpretation of the results.

Future studies should examine, whether reduced cognitive processing speed constitute vulnerability markers or cognitive scars and evaluate its impact on severity and/or development of depressive symptoms. Identifying cognitive vulnerability traits or scars of SAD would require that researchers

follow individuals at risk of developing SAD over a long-term, period; starting before disorder onset and following individuals over the course of their illness and into remission. If working memory and cognitive processing speed indeed are antecedents for the development of SAD, and cognitive processing speed is involved in the seasonal change in SAD depressive symptoms, clinicians and researchers could use this information to advance our understanding of the etiology of SAD. In particular, cognitive processing speed could be used as a screening tool to identify individuals at risk of developing a SAD depression before it occurs.

A relevant concern when addressing the involvement of cognitive vulnerability markers or cognitive scars in SAD is the stability of these factors. Rohan and Rough (2017) raises the possibility that *"SAD-related vulnerabilities may differ in presence and perhaps even differ across episodes within individuals"* (Rohan and Rough, 2017, p. 259). If this holds true, it could help explain why the stability of the SAD diagnosis has been shown to vary. Lam et al. (2001) polled data from four longitudinal follow-up studies on SAD, and showed that approximately 28-44% of the individuals original diagnosed with SAD developed either non-seasonal depressions, or continued to present with depressive symptoms in the summer, 14-38% either developed subsyndromal SAD or went into clinical remission while 22-42% continued to present with SAD (Lam et al., 2001). This also underline that results from a neuropsychological test reflects a "snapshot" assessment at a certain point in time.

Neuroticism and Extraversion as vulnerabilities to SAD

We found that high levels of Neuroticism reported during the remitted phase were related to depression severity during the symptomatic phase in the SAD group. Importantly, this association was not present in the healthy control group. We also found an increase in Neuroticism (including angry and hostile attitudes, depression and vulnerability to stress) and a decrease in Extraversion (including positive emotions) from summer to winter in individuals with SAD compared to controls. It is possible that these findings signify two different kinds of mechanisms relevant for a vulnerability perspective. *(1)* The association between Neuroticism during remitted phase and symptom severity during the depression, suggest that a high level of Neuroticism during the remitted phase is important for the severity of depressive symptoms during a depressive episode. Although Neuroticism is a robust personality trait that constitutes a risk factor for depression (Christesen and Kessing, 2006; Kotov et al., 2010; Malouff et al., 2005), we did not observe higher levels of Neuroticism during remission in SAD compared to controls. As such, Neuroticism may not represent a vulnerability trait specific for SAD per se, but our results imply that those individuals with high Neuroticism in the

SAD group during the symptom free phase, were more likely to develop severe depressive symptoms in response to the change of season during winter. *(2)* Based on the aforementioned findings of seasonal changes in Neuroticism and Extraversion in individuals with SAD, it is possible that these personality traits, reflect vulnerabilities in SAD by representing markers of inefficient self-regulation processes that are enhanced as winter approaches, although this remains to be clarified in future studies. As such, catastrophic negative thoughts about the coming winter together with an increased vulnerability (personality) profile could give rise to SAD symptoms. Information on changes at the very core of SAD individuals' perceived mind during a depressive episode could be employed in a therapeutic context. For example, when offering psycho-education this information could be used to give the individual with SAD a more nuanced view on their self-perceived mind outside and during a depressive episode. Moreover, motivating individuals with SAD to do things they enjoy brightening their lives during the winter months, could change the behavioural manifestations of the self-perceived change in personality characteristics and thus prove effective against SAD.

In summary, from a clinical point of view, treatment that not only target the overt affective symptoms during symptomatic the phase but also seek to improve cognitive processing and lowering emotion regulation difficulties associated with high levels of Neuroticism levels during the remitted phase could prove valuable for reducing SAD depressive symptoms.

Self-report bias or can personality really change?

A weakness in any self-reported personality measure is the risk of measuring the self-perception of personality instead of measuring the underlying personality traits (a self-report bias). As previously mentioned, we found that Neuroticism and Extraversion scores were higher during the acute depressive episode than when assessed during remission for individuals with SAD. From these results, it is likely that the personality assessment during winter is affected by the individual's level of distress and does therefore not accurately reflect the "true" underlying personality. Supporting this notion is a study showing that reduced recall of positive versus negative personality characteristics characterized individuals with SAD and S-SAD compared to controls (Harmer et al., 2012). As such, we speculate that the seasonal changes in Neuroticism and Extraversion scores may simply reflect changes in state rather than personality trait levels, although this cannot be examined with this data. I acknowledge that different variables (e.g. depressive symptoms) could be relevant for explaining why individuals with SAD in this study, report higher scores on Neuroticism and lower scores on Extraversion in winter compared to summer. However, the aim of this study was not to explain *why* the individuals with SAD perceive their personality different in winter compared to summer, in

comparison to healthy controls, but to show that this change in self-perceived personality occur in SAD. Ultimately, if the seasonal-related changes in Neuroticism and Extraversion truly reflect changes in state rather than trait levels, this should not be considered a limitation, but rather as valuable information, since this provides insight into how currently depressed individuals with SAD subjectively portray their anxiety, angry and hostile attitudes, depression, current vulnerability to stress and their lack of positive feelings. Thus, examining personality during the symptomatic phase in SAD may not necessarily clarify the underlying SAD etiology, but could prove helpful for clinicians in understanding and relating to their patients.

Openness as a vulnerability to SAD

In the SAD literature, higher levels of Openness have been found to characterize individuals with SAD compared to non-seasonal depressed individuals and norm data (Enns et al., 2006). From these results, it has been proposed that higher scores on the trait Openness could leave some individuals more vulnerable to experience a heightened sensitivity to the environmental stress of winter. For example, it has been argued that individuals with high levels of Openness may experience normal mood fluctuations more intensely and may be more inclined to explain these mood fluctuations as being caused by external factors such as the lack of sunlight (Bagby et al., 1998; Murray et al., 2002).

Contrary to our hypotheses in study 3, individuals with SAD did not exhibit higher scores on Openness compared to controls in both summer and winter, and nor did individuals with SAD differ in their Openness scores in summer versus winter. It should be noted that the Openness scores reported by the healthy controls in our study were significantly higher in both summer and winter compared to Openness scores reported by 600 healthy Danish individuals (Costa et al., 2003) (Openness in summer 120±16 and winter 121±14 vs. 105±19, mean±SD, p-values<.001. Alpha was set at $p \leq .005$ for conducting ten independent sample t-tests: Five FFM traits*two seasons [winter, summer]), probably reflecting that our healthy controls all volunteered for a research study. Higher scores on Openness in healthy controls involved in research studies compared to Danish FFM norm data have previously been reported (Frokjaer et al., 2008). This may have influenced our ability to detect group and group-by-season differences for Openness as our healthy controls resembled the proposed profile of high trait Openness in SAD.

Protective factors for SAD

Invulnerability, protective factors and resilience are terms frequently used to describe the opposite dimension of vulnerability, and each term suggests a resistance to develop psychopathology in the presence of a stressor (Ingram and Luxton, 2005). In a study by Zammit et al. (2004), low IQ was

related to an enhanced risk for developing future depressive episodes, suggesting that enhanced premorbid cognitive abilities may protect individuals from developing depression. Interestingly, the healthy controls in our study showed a better inhibition of angry faces during winter compared to summer, which could not be explained by a test order effect, as the groups were counterbalanced to season of first test session. One possible interpretation of these findings is that better inhibition of inappropriate responses to negative information in winter, reflects an ability to negate the environmental stress of winter, and we speculative that it could act as protective factor for those at-risk of developing SAD. If a better inhibition of irrelevant negative material to a certain degree, counterbalance the impact of vulnerability to SAD, intervention targeting protective factors could potentially prove relevant. A subset of the sample used in this study, was also included in a larger positron emission tomography study, published in (Mc Mahon et al., 2016). In this study, we showed that in the winter, females with seasonal affective disorder upregulate the serotonin transporter whereas healthy females downregulate the serotonin transporter. An interpretation across these study findings is that SAD-resistant individuals (i.e. individuals with low seasonality scores) may be better to appropriately adjust their inhibitory control and serotonin transporter binding levels to accommodate the stress of winter, and thereby protecting against the symptoms of SAD.

The relation between cognitive functions

Reduced cognitive processing may mediate the SAD-related working memory deficits (study 2), suggesting that reduced cognitive processing constitutes a lower-order mechanism responsible for much of the higher-order working memory deficits in SAD. This interpretation is supported by studies showing that processing speed act to facilitate the effective execution of higher-order cognitive operations (Mathews, 2011; Nebes et al., 2000; Salthouse, 1996). Thus, therapies targeting specific areas of cognition, e.g. cognitive remediation therapy (Richard et al., 2013), could be an appropriate strategy in rehabilitation of cognitive impairments in SAD.

A post-hoc cross-study analysis revealed that working memory and cognitive processing speed were not significant predictor variables for the observed SAD-related impairments in inhibition of angry and sad faces. Although replications of these results are warranted, the results suggest that inhibitory control (measured with Emotional Go/NoGo task) do not seem to be dependent on working memory (measured with LNS) and cognitive processing speed (measured with SDMT) in our study participants. Another more methodologic interpretation is that performance on the Emotional Go/NoGo task relies little on working memory and cognitive processing speed, as the demand on keeping information of the target stimuli active in memory is low. This has previously been suggested

by Diamond (2013) and is in line with the hypothesis put forward by Nebes et al. (2000) stating that "*…rather than depressed patients having focal deficits on a variety of cognitive abilities, the likelihood that they will be impaired on a particular task is a function of the degree to which that task is dependent upon processing speed and working memory for its efficient performance*"(Nebes et al., 2000, p. 688). Knowledge on how cognitive functions are related to one another could provide important information for understanding the etiology of cognitive impairments in SAD and should be explored in future research.

SAD etiology: Integration of study findings

The Integrative Cognitive-Behavioural model by Rohan (2009) integrates psychological, biological and behavioural vulnerabilities to understand SAD onset, maintenance and remission (Rohan and Rough, 2017). In the following, only the results of SAD-related impairments in working memory and cognitive processing speed and the SAD-related seasonal changes in Neuroticism and Extraversion, will be discussed within the framework of the Integrative Cognitive-Behavioural model, as these characteristics could constitute SAD vulnerabilities, as previously suggested. To what degree cognition and personality are related constructs have been intensely debated in the research literature (Zeidner and Matthews, 2000). Although this association remains to be clarified, I suggest in the following that cognition (i.e. working memory and cognitive processing speed) and the seasonal changes in Neuroticism and Extraversion induce SAD depressive symptoms through different pathways in the Integrative Cognitive-Behavioural model.

Season-independent impairments in working memory

In regard to the season-independent impairments in working memory and cognitive processing speed, I speculate that a reverberating cycle between these cognitive mechanisms and physiological vulnerabilities initially are precipitated by a more physiological process in reaction to an environmental stressor. As discussed in the section "Trait-like and state-dependent markers of SAD" (page 57-58), the physiological mechanisms interacting with working memory and/or cognitive processing speed may include altered functioning of regions and/or brain structures sub-serving these cold cognitive functions, for example the prefrontal cortex and its associated brain regions. As such, the combination of cold cognitive impairments and prefrontal abnormalities might act to increase vulnerability towards developing SAD depressive symptoms.

Seasonal changes in Neuroticism and Extraversion

I suggest that the combination of increased Neuroticism and decreased Extraversion from summer to winter, activated by a more reactive psychological process (i.e. negative anticipations of winter), may set the stage for an onset of a SAD depressive episode, marked by reduced positive emotionality. As such, the negative anticipations of winter may increase angry and hostile attitudes towards others as well as increase the tendency to experience depression, vulnerability and anxiety, reinforcing reduced engagement with the external world as winter approaches (and vice versa); this combined with a social pattern of less frequent positive emotions, and a lower activity level in winter compared to summer, may add an important aspect of vulnerability for depressive episodes in SAD because it lowers the rate of positive reinforcement.

The exact physiological mechanisms interacting with these personality traits are largely unknown, but may include maladaptive brain activation during fear learning and anticipation of aversive stimuli. This statement is supported by studies showing that individuals with high levels of Neuroticism display increased activation in brain areas related to fear learning, including the hippocampal–parahippocampal complex, and decreased activation in brain regions related to anticipation of aversive stimuli, including anterior cingulate cortex and striatum (For a meta-analysis see Servaas et al. (2013). Whether highly neurotic individuals with SAD display similar brain activation patterns remains to be clarified, but if so, it might explain why these individuals form associations between perceived negative stimuli and environmental cues signalling the change towards winter season. Somewhat in support of this statement, are studies showing that individuals with SAD exhibit distinct patterns of emotional and psycho-physiological reactivity to light and winter-related cues compared to controls (see Rohan et al. (2009) for review). As such, a combination of inefficient self-regulation strategies, a hypersensitive fear conditioning system, and an altered anticipatory process in those high in Neuroticism could point to mechanisms relevant for SAD development.

Based on the findings in study 1-3, I suggest that reduced working memory and cognitive processing speed independent of season as well as the increase in Neuroticism and decrease in Extraversion from summer to winter, and high Neuroticism scores in summer could be added to the Integrated Cognitive-Behavioural model of SAD proposed by Rohan (2009) (see Figure 11).

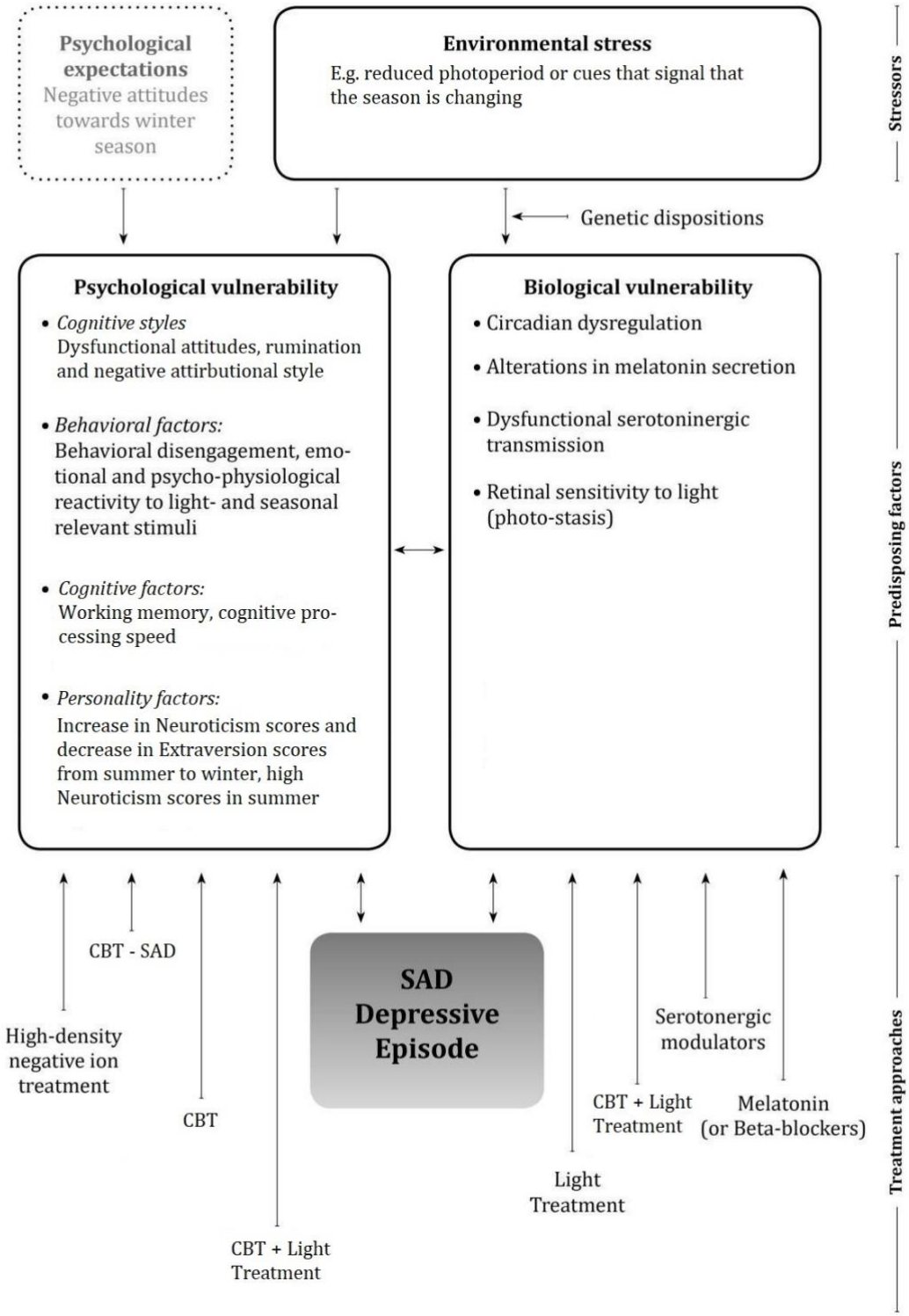

Figure 11. An example of a diathesis-stress model of SAD by Liv Vadskjær Hjordt. *Notes:* The model is similar to the Integrative Cognitive-Behavioural model of SAD proposed by Rohan (2009), but adds the potential role of impairments in cold cognitive functions (working memory, cognitive processing speed and motor speed) and seasonal changes in Neuroticism and Extraversion in SAD. The outlined treatment approaches intervening with the psychological and psychological vulnerabilities are not comprehensive. Abbreviations: CBT = Cognitive Behavioural Therapy, CBT-SAD = Cognitive Behavioural Therapy tailored for SAD.

Can our findings on SAD be generalized to MDD?

Will individuals with non-seasonal depression show similar cognitive impairments, personality characteristics and seasonal changes in Neuroticism and Extraversion as the individuals with SAD in our sample? And will SAD share vulnerabilities to non-seasonal depression across depression sub-types? It is not possible to answer these questions with our data, as we did not include a non-seasonal depressed control group. Longitudinal studies comparing cognitive performance in SAD with that of non-seasonal depression both in symptomatic and symptomatic-free phase would constitute a completely different and quite unpredictable study design compared to the study design applied in study 1-3. By nature, the first investigation of individuals with non-seasonal depression would need to be in the depressed state and the follow-up would be at variable time intervals after the first investigation. In addition, the individuals would most likely have undergone one or more treatment attempts to remit from the depressive episode. Thus, results derived from such a study may be influenced by factors that would make it difficult to infer something about the stability of these cognitive impairments across depression sub-types, or whether our results were specific to SAD. Also, whereas non-seasonal depression is a heterogeneous disorder in which a number of underlying presentations may share a common phenomenology, but have different etiologies (Goldberg, 2011), SAD may be a more homogenous syndrome, making it difficult to directly compare SAD with non-seasonal depressions populations.

Since SAD in our study is classified as a form of recurrent major depression (WHO, 1994), we find it likely that individuals with SAD and non-seasonal depression are similar with regard to their affective state during the depressive episode, which could imply 'shared' (cognitive and personality) vulnerabilities to the development of affective symptoms across depression sub-types. This line of thinking is consistent with Lam et al. (2001), who argue that SAD and non-seasonal depression share vulnerabilities for depression, but that individuals with SAD also have a vulnerability with regard to experiencing seasonality. Yet, the clinical manifestation of SAD is typically different from that of non-seasonal depression, since individuals with SAD, more often than individuals with other types of depression, report atypical vegetative symptoms, such as hypersomnia, increased appetite or carbohydrate craving, and weight gain (McCarthy et al., 2002; Partonen and Rosenthal, 2010; Tam et al., 1997). Although it remains to be clarified whether or not these vegetative symptoms influence cognition and personality in SAD, two studies have reported that higher levels of rumination were associated with a stronger relationship between cognitive-affective and vegetative symptoms in SAD (Young et al., 2008), suggesting that cognition and vegetative symptoms are somehow related. The

question as to whether our findings on SAD can be generalized to non-seasonal depression awaits clarification in future studies.

The following sections include strength and main methodological considerations across all three studies, a conclusion and an outline of future research perspectives.

Study strengths and study limitations

Study strengths

The studies included in this thesis have several strengths. *Firstly*, the study design was longitudinal and seasonal counterbalanced. The participants were well-characterized and homogenous individuals diagnosed with SAD, who presented with full remission in summer, and had not received BLT or psychotropic drugs during the course of study and within the past year. The longitudinal study design effectively reduces the intra-individual differences, as participants in both groups act as their own controls, and the homogeneous study population increases the statistical power of detecting a hypothesized effect. *Secondly*, the strict inclusion criteria of a low GSS score in the healthy control group ensured the absence of seasonality, which otherwise could have blurred subtle seasonal changes in hot and cold cognitive processing. *Thirdly*, the use of an extensive set-up of well-validated, reliable and sensitive psychometric cognitive tests allowed for an objective detection of cognitive impairments associated with SAD that otherwise are not directly clinically observable. *Lastly*, we adjusted SDMT performance for the potential confounding effect of SRT performance, which is relevant when addressing cognitive processing speed in SAD using tasks that both require cognitive and motor processes.

However, the findings reported in paper 1-3, must be interpreted under some methodological limitations.

Study limitations

The use of SAD-resilient healthy controls

We included a particular cohort of resilient healthy controls; they were relatively young, presented with low GSS scores and did not present with current or a history of psychiatric illness, or a family history of mood disorders. This may have biased our healthy sample towards a group that were resilient to the environmental stress of winter and with a low risk of developing SAD related depressive symptoms. This was also mirrored by the high vocational educational scores in both groups, many of which were university students, indicating a high socio-economic status for most

study participants. Thus, our findings are not representative of the larger Danish population in terms of health and educational level and may have underestimated potential cognitive impairments in more vulnerability individuals, e.g. individuals recovered from psychiatric illnesses or with first-degree relatives with mood disorders.

The use of untreated SAD individuals without psychiatric comorbidity

We used very strict medication inclusion criteria. Although this allowed us to examine SAD in a naturalistic way, these factors may have introduced a sampling bias with a SAD group presenting with less severe SAD depressive symptoms, which could have underrated the degree of cognitive impairments compared to a more representative SAD-sample. However, it is our clinical experience that many individuals with SAD often choose to withhold from psychopharmacological treatment, because they have experienced that their depression is seasonally reversible. In addition, none of the individuals with SAD that were included in the summer dropped out the following winter, because of the criteria requiring individuals with SAD to abstain from starting up treatment. Thus, in regard to treatment characteristics, we do not believe that the SAD sample in this study is very different from other individuals diagnosed with SAD in Denmark. We also used very strict comorbidity exclusion criteria. Although this allowed us to examine cognition in SAD without the interference of other psychiatric disorders, this may again have introduced a sampling bias with a SAD group presenting with less severe SAD cognitive impairments.

The (lack of) ecological validity of the neuropsychological tests

Since neuropsychological tests typically involve discrete responses to single events and are carried out in carefully controlled settings with little or no stress and disturbances results from such tests should be considered a "snapshot" at cognitive functioning a certain point in time. In line with this, it is still being debated whether traditional neuropsychological tests can predict anything about real life cognitive dysfunctions, and as such there has been an increased focus on the ecological validity of cognitive tests (Dawson and Marcotte, 2017). Hence, how the individuals with SAD in our study perform on the neuropsychological tests may not be representative over long time periods or give a clear indication of how individuals perform in stressful and demanding situations, and it is possible that the level of cognition functioning may be worse in real life settings compared to a test setting. This latter notion is especially important since most currently depressed individuals with SAD work or study despite experiencing SAD depressive symptoms.

Do cognitive tests measure one or more cognitive domains?

Very often neuropsychological tests are described to assess one or two specific cognitive domains of brain functioning. This may be an oversimplification, as for almost all neuropsychological tests, successful performance depends on intact functioning of several supporting cognitive domains. For examples; In our study, the SRT is widely considered to measure simple motor processes. However, successful performance on this simple task may also requires participants to focus attention at the location where the white square will be presented on the computer screen, and some decision making in regard to the trade-off between being fast but accurate. Moreover, although SDMT in the literature is generally considered to be a test measuring cognitive processing speed, successful performance on this task is also dependent on functional integrity of several cognition functions, such as attention, working memory and executive functions (Harrison, 2016, p. 230). In addition, common for all cognitive tests is that test performance relies on whether participants understand and remember the instructions given by the tester. This highlights the need for future studies to replicate our findings by using different neuropsychological tests that also target working memory and cognitive processing speed.

Computer versus paper - does it make any difference in test performance?

Using both computer and paper-and-pencil tests in our study raises the question if computer-based tests influence test performance differently than paper-and-pencil tests. In our studies, the cognitive functions measured with computer appear to be more state-like characteristics of SAD, whereas the cognitive functions measured with paper-and-pencil tests appear to be more trait-like. Our data cannot address whether this is explained by the mode of test administration or it is by chance, but we think the latter is more likely.

The use of self-report measurement

Although the NEO PI-R and the MDI questionnaires are perceived as golden standards when examining personality characteristics and the level of depressive mood in both clinical and healthy samples, these questionnaires rely on self-examination. Biased self-reporting is an important concern in research relying on questionnaires and refer to that data may be influenced by e.g. a lack of introspective ability to provide an accurate response to a question, censorship, social desirability, situational aspects or by a systematic manipulation of answers on items (Domino, 2006). However, as reported in paper 1, we found a significant positive correlation between the objectively rated SIGH-SAD scores, and the subjectively reported MDI scores in both summer and winter, suggesting that the participants with SAD accurately perceive their depressive symptoms.

Sample size

The relatively small sample size may have limited our statistical power in all three studies and could for example explain our statistically non-significant group findings on Neuroticism, Openness and Extraversion in summer, and increases the false-discovery rate (type-II error).

CONCLUSION AND FUTURE RESEARCH PERSPECTIVES

The overall aim of this thesis was to examine the complex interplay between seasonal changes, cognition and personality. In particular, we utilized SAD, which because of its predictably recurring pattern of depressive episodes, facilitates the study of trait-like and state-dependent factors within cognition and personality. With individuals suffering from SAD and matched healthy controls, we tested the effect of summer and winter on inhibitory control, emotional face identification, working memory, cognitive processing speed, motor speed and self-perceived personality. Although we advocate that independent replications are warranted, our results suggest that individuals with SAD are characterized by both trait-like and state-dependent cognitive impairments and seasonal changes in self-perceived personality. More specifically, we found that impaired inhibition of angry and sad faces, reduced identification of happy faces, high levels of Neuroticism and low levels of Extraversion characterized individuals with SAD in winter compared to healthy controls, and thus may constitute sensitive state markers of SAD pathology. Moreover, we found that impaired working memory, cognitive processing- and motor speed may constitute more trait-like characteristics of SAD, as these impairments did not change as individuals with SAD moved from their depressive phase to their asymptomatic phase. In addition, the slowed lower-order processing speed appeared to account for most of the working memory impairments observed in the SAD group. The association between reduced cognitive processing speed independent of season, and the change in depressive symptoms from summer to winter, supports this interpretation of cognitive processing speed being a trait-like marker of SAD. Moreover, we found that in winter, individuals with SAD scored higher on Neuroticism and lower on Extraversion compared to their own summer scores. We interpreted these findings to signify that individuals suffering from SAD experienced seasonal fluctuations at the very core of their self-perceived personality. Finally, our results also point to the value of using trait Neuroticism during remission to identify individuals vulnerable for developing more severe SAD depressions, since high levels of Neuroticism during the remitted phase, were related to depressive symptoms in SAD.

Our findings provide a psychological link between cognitive mechanisms and personality characteristics and SAD. This could guide future longitudinal studies aiming to study which psychological factors are involved in the development of SAD.

Research perspectives

Recommendations for future studies on SAD

The limitations and findings of this study, point to some recommendations for future studies on SAD:

- In general, independent replications of our findings are warranted given the paucity of SAD studies on hot and cold cognition measured longitudinally with neuropsychological tests.
- Our results from study 2, underline the importance of adjusting for cognitive variables known to affect the cognitive function in question. More specifically, researchers who wish to examine working memory performance in SAD are recommended to adjust for the potential confounding effect of a slowing in cognitive processing speed. This kind of adjustment could provide a more nuanced picture of how cognition is involved in SAD.
- It would also be relevant to combine standard conventional neuropsychological tests (i.e. computer and/or paper-and-pencil) with cognitive tests that have a greater ecological validity. Such tests may be better suited to illustrate the cognitive impairments that individuals with SAD experience in everyday life.
- It could be interesting for future researcher to include an observer form of the NEO PI-R, making it possible to compare the patient's self-rating of personality with the more objective ratings from i.e. close family members. Observer ratings, such as these could provide an independent source of information about individuals with SAD that are not contained by self-reported response bias, and could give a more nuanced perspective of the personality in SAD, which could be valuable from a clinical and a research perspective.
- From the reviewed literature and from the studies supporting the conceptual models of SAD (Rohan, 2009; Young et al., 1991), it is clear that SAD is a multifaceted phenomenon resulting from complex and dynamic interactions of several vulnerability factors. Therefore, I encourage SAD researchers to collaborate across disciplines, e.g. collaborations between researchers working in the field of genetics, neurobiology, psychiatry, clinical psychology and neuropsychology. More interdisciplinary integrative approaches to the study of SAD are vital to the understanding of how the transition from summer to winter interacts with underlying vulnerabilities, to trigger the development of SAD in some individuals, and to

advance the development of more efficient treatments, and to better target prevention strategies.

A future study on SAD

With an eye to future research; our findings of seasonal independent cold cognitive impairments and seasonal related changes in personality, encourage me to further study: (1) Seasonal changes in personality and cognitive status as well as cognitive change over time in individuals 'at risk' or with sub-clinical levels of SAD. (3) Vulnerabilities involved in the initial development of seasonal symptoms. In the following I briefly outline my thoughts about a future SAD study that could elucidate some of the above-mentioned research themes.

Study participants and design

I wish to longitudinally investigate individuals who do not presently pose with SAD, but who exhibit certain behaviours hypothesized to make them vulnerable to develop SAD. Based on our study findings it could for example include healthy individuals but who exhibit season-independent impairments in working memory, cognitive processing speed or who report large seasonal changes in self-perceived personality traits. However, perhaps a more relevant cohort to study is individuals with S-SAD since such individuals have a history of seasonal problems and therefore may be more vulnerable to develop SAD depressive episodes. Individuals with S-SAD could be identified using the so-called Kasper criteria (Kasper et al., 1989)[6]. In order to get more knowledge about the developmental aspects of SAD, I wish to include individuals with S-SAD between 16-20 years of age, since the mean age of the onset of SAD is between 20-30 years (Magnusson, 2000). I wish to include ~60 individuals with S-SAD and ~60 age-, gender and education matched healthy controls. In >5 consecutive years all participants will be assessed twice; once in summer and once in winter. Individuals will S-SAD will be interviewed by trained psychiatrists in summer and in winter in order to evaluate the presence of a SAD diagnosis and comorbid disorders.

Psychological assessment instruments

The following describes my thoughts about which psychological instruments that could be interesting to include at the test sessions, although I am aware that repeated test administration can give rise to

[6]Criteria for identifying individuals with S-SAD: 1) as GSS score of 10 or above, but no or mild problems with seasonal changes; 2) a GSS of 8 or 9, but who experience seasonal changes as either a problem or not (Kasper et al. 1991)

practice effects. Participants will complete the same neuropsychological tests and self-report questionnaire as described in this thesis. As an adjunct to these more traditional neuropsychological tests, I wish to include assessment where cognitive functioning is directly evaluated through everyday life situations. This is relevant since the examination of cognition in real-life settings appear to have a better predictability of real life cognitive dysfunctions (Alderman et al., 2003). Such assessments could involve dual-task walking (DTW) paradigms, which combine walking (e.g. treadmill or ground walking) and cognitive talking-types tasks (e.g. LNS or word fluency tasks) (McFadyen et al., 2017). It could also involve performance-based tasks in real world settings, such as the Multiple Errands Test (MET) by Alderman et al. (2003). This paradigm evaluates the effect of cognitive impairments on everyday functioning through the use of four simple real-world tasks; buying specific items (e.g. bread and birthday cards), collecting and recording items of specific information (e.g. library closing time), arriving at a stated location 20 minutes after beginning the test) and telling the assessor when the participant finished the task.

As an adjunct to the self-reported NEO PI-R questionnaire used in this thesis, I wish to invite SAD relatives to fill out an observer rating (Form R) of the short form of NEO PI-3 (McCrae and Costa, 2007). This could provide a more objective evaluation of the seasonal changes in Neuroticism and Extraversion reported by the individuals with SAD in our study. To study whether or not learned negative anticipations of winter develops over time in individuals with S-SAD and whether they interact with psychological or biological factors to develop a SAD episode, I would like to use Rohan et al.'s psychophysiological task (Rohan et al., 2003) which measure skin conductance and depressive mood in response to slides of varying light intensity. Finally, I will collect data on the functional polymorphisms of the SERT gene (5-HTTLPR), where the S- and Lg-allele have been associated with SAD (Rosenthal et al., 1998). The genotype status will be used to investigate gene-by-environment interaction effect on neuropsychological and personality measures.

The outlined study design allows for the examination of the antecedence and stability or progress of the hypothesized vulnerability factors in groups of individuals who currently do not experience SAD, but could also give empirical support of hypotheses underlying conceptual models of SAD, e.g. the Integrative Cognitive-Behavioural model of SAD (Rohan, 2009) or The Dual-Vulnerability model of SAD (Young et al., 1991).

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APPENDICES

Paper 1: State-dependent alterations in inhibitory control and emotional face identification in seasonal affective disorder

Paper 2: Season-independent cognitive deficits in seasonal affective disorder and their relation to depressive symptoms

Paper 3: Personality characteristics in seasonal affective disorder and their implications for severity of depression

ICD-10 diagnostic criteria for a depressive episode