Tampere University

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Temperament and Character in Depression, Anxiety, and Alcohol Use Problems

Tampere University Dissertations 208

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ACADEMIC DISSERTATION
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To my Fellowmen

ABSTRACT

Background. Not enough is known about which patients suffering from major depressive disorder (MDD) benefit from antidepressant drug treatment or how temperament and character are associated with response to antidepressive treatment, long-term depression outcome in patient populations with substance use and anxiety disorder comorbidities. Earlier studies have shown that individual temperament is associated with psychiatric morbidity, outcome of depression, anxiety disorders, and substance use. However, no prior studies have addressed whether temperament clusters 1) predict antidepressive treatment response, 2) anxiety disorder comorbidity or 3) how vegetative symptoms of depression modulate the temperament clusters effect on response to antidepressive treatment. So far the available data on the differences in temperament and character profiles of depressed patients with or without harmful drinking has been limited. Moreover, it is not well known how harmful alcohol use modifies the effects of temperament and character on depression outcome. Knowledge of these associations could provide a method for enhancing more individualized treatment strategies for the diverse depressed clinical populations in psychiatric secondary services.

Materials and Methods. For Study I we recruited one hundred Finnish outpatients in Tampere region, Southern Finland (aged 19 to 72) suffering from MDD, of whom 86 completed the 6-week Pharmacogenetic Study on Depression (DEPGEN). We assessed their temperament features at baseline with the Temperament and Character Inventory (TCI) and used cluster analysis to determine the patients' temperament profiles. We also categorized the patients according to the vegetative symptoms of MDD, i.e. reduced sleep and appetite and inner tension. General linear models (GLMs) were used for analyzing the association between temperament clusters and endpoint depressive symptoms measured by Montgomery Åsberg Depression Rating Scale scores (MADRS).

For Studies II-IV we screened 242 depressed patients with at least moderate level of depressive symptoms (BDI $\geq$ 17) admitted to psychiatric secondary services in South Ostrobothnia region in Finland and giving their consent to participate in the Ostrobothnia Depression Study (ODS). The Alcohol Use Disorders Identification

Test (AUDIT) was used for identifying patients with marked alcohol use problems (AUP, AUDIT ≥ 11).

For Study II 127 depressed patients without alcohol use problems (non-AUP) and 89 depressed patients with alcohol use problems (AUP) were eligible for the main analyses. We assessed all patients using the Temperament and Character Inventory (TCI-R) at baseline and after 6 weeks of treatment. Using univariate general linear models (GLMs), we analyzed differences in TCI-R between AUP and non-AUP. GLMs were also used in analyzing the associations between TCI-R changes and antidepressive treatment responses measured with ΔMADRS.

For Study III 173 patients were assessed using the MADRS and the TCI-R after 6 weeks of antidepressive treatment. Outcome of depression (MADRS scores across three follow-up points at 6 weeks, 6 months and 24 months) was predicted by AUP, gender, and AUP x Gender and AUP x Time (Time = repeated measures variable) interactions together with temperament and character dimension scores in a linear mixed effects model.

For Study IV 204 patients were assessed with the TCI-R and their diagnoses with the Mini International Neuropsychiatric Interview. Two-step cluster analysis was used for defining patients' temperament profiles and logistic regression analysis was used for predicting different anxiety disorders for various temperament profiles.

Results. Study I resulted in finding an association between skewed temperament profile (deviations from the average general population scores in different temperament dimensions) and severity of MDD, but the temperament profiles alone did not predict antidepressant treatment response. Those with higher baseline vegetative symptoms score had modest treatment response. The best fitting model with baseline MADRS vegetative symptom scores, age and temperament clusters as explanatory variables explained 20% of the variance in the endpoint MADRS scores.

In Study II alcohol use problems independently explained significant proportions of the variation in Novelty Seeking, Self-Directedness, and Persistence. Reward Dependence score change explained 14% of the ΔMADRS in AUP, while a similar model was non-significant in predicting ΔMADRS in non-AUP. Character score changes in Self-Directedness and Self-Transcendence combined explained 13% of ΔMADRS in non-AUP, whereas they were all non-significant in AUP. AUP patients had lower Self-Directedness and Persistence and higher Novelty Seeking scores than non-AUP patients.

In Study III poorer outcome of depression (MADRS scores at 6 weeks, 6 months and 24 months) was predicted by AUP × Time interaction ($p<0.001$) together with

low Reward Dependence (p=0.003). Gender and all other temperament and character traits were non-significant predictors of the depression outcome in the mixed effects model.

The cluster analysis in Study IV resulted in finding four temperament clusters: 1) Novelty seekers with highest Novelty Seeking scores (n=56), 2) Persistent with highest Persistence scores (n=36), 3) Reserved with lowest Novelty Seeking scores (n=66) and 4) Wearied with highest Harm avoidance, lowest Reward Dependence and lowest Persistence scores (n=58). After adjusting for clinical variables, panic disorder and/or agoraphobia were predicted by Novelty seekers' temperament profile with odds ratio [OR]=3.5 (95% confidence interval [CI]=1.8−6.9, p<0.001), social anxiety disorder was predicted by Wearied temperament profile with OR=3.4 (95% CI=1.6−7.5, p=0.002), and generalized anxiety disorder was predicted by Reserved temperament profile with OR=2.6 (95% CI=1.2−5.3, p=0.01).

Conclusions. The temperament clusters were associated both with severity of depression and antidepressive treatment response of depression. The effect of temperament profile alone was modest but, combined with vegetative symptoms of depression, their explanatory power was more marked, suggesting a possible association of these two in the biological basis of MDD. (I)

The changes detected in Reward Dependence over 6 weeks of antidepressive treatment and lower Self-Directedness in AUP patients could be indicative of different biological mechanisms associated with depressive symptomatology in patients with harmful alcohol use. Changes in character are associated with acute treatment response in non-AUP. (II)

Possibly due to the modifying effect of alcohol use problems, high Reward Dependence was associated with better antidepressive treatment outcome over the two-year follow-up. Harm Avoidance and Self-Directedness did not predict depression outcome when alcohol use problems were controlled for. (III)

Novelty seekers temperament was associated with panic disorder, Reserved with generalized anxiety disorder, Wearied with social anxiety disorder, and Persistent with lower risk of anxiety disorder comorbidities. These results suggest that TCI-R could offer a valuable dimensional method for predicting the risk of anxiety disorders in diverse depressed patients. (IV)

TIIVISTELMÄ

Tausta. Tieto siitä ketkä masennuspotilaat hyötyvät masennuslääkityksestä tai siitä, miten temperamentti ja luonnepiirteet ovat yhteydessä masennuksen hoitotulokseen potilailla, jotka kärsivät samanaikaisesta ahdistuneisuushäiriöstä tai päihdehäiriöistä on puutteellista. Aiemmat tutkimukset ovat osoittaneet, että yksilöllinen temperamentti on yhteydessä psykiatriseen sairastavuuteen, masennuksen hoitotulokseen ja ahdistuneisuushäiriöihin, sekä päihdekäyttöön. Aikaisempi tutkimus ei kuitenkaan ole käsitellyt sitä, ovatko temperamenttiprofiiliklusterit 1) yhteydessä masennuslääkevasteeseen, 2) ahdistuneisuushäiriöiden samanaikaissairastavuuteen tai sitä 3) onko masennuksen vegetatiivisilla oireilla kuten ruokahaluttomuus tai unen häiriöt vaikutusta temperamenttiprofiiliklusterien mahdolliseen assosiaatioon masennuksen hoitovasteen kanssa. Tähän saakka tieto on ollut vähäistä myös siitä, millaisia mahdollisia eroja masennuspotilaiden temperamentti- ja luonnepiirreprofiilien välillä on alkoholin riskikäyttäjillä verrattuna alkoholia vähemmän käyttäviin. Uutta tietoa tarvitaan myös siitä, muokkaako alkoholin haitallinen käyttö temperamentti- ja luonnepiirteiden yhteyttä masennuksen hoitotulokseen. Näiden yhteyksien parempi tuntemus voisi auttaa yksilöllisten hoitostrategioiden kehittämisessä erilaisista oirekuvista kärsivien masennuspotilaiden psykiatrisen erikoissairaanhoidon suunnittelussa.

Aineisto ja menetelmät. Tutkimusta I varten rekrytoitiin 100 suomalaista avohoidon masennuspotilasta Tampereen seudulla (iältään 19–72-vuotiaita), jotka osallistuivat masennuksen farmakogenetiikan tutkimukseen (DEPGEN-tutkimus). Näistä potilaista 86 pysyi tutkimuksessa 6 viikon seuranta-ajan loppuun saakka. Potilaiden temperamenttiominaisuudet määritettiin alkutilanteessa Temperament and Character Inventory -kyselyllä (TCI) ja tilastollista klusterianalyysia käytettiin potilaan temperamenttiprofiiliklusterien määrittämiseksi. Potilaiden masennusoireiden vegetatiivinen oirekomponentti määritettiin myös alkutilanteessa tilastollista analyysiä varten. Masennusoireiden mittarina tutkimuksessa käytettiin Montgomery Åsbergin masennusoirehaastatteluissa (MADRS) saatuja pistemääriä. Tilastollisia monimuuttujamalleja (GLM) käytettiin temperamenttiklusterien ja masennusoireiden loppupistemäärän välisen yhteyden analysoimisessa.

Tutkimuksiin II-IV seulottiin Etelä-Pohjanmaan alueella 242 vähintään keskivaikea-asteisista masennusoireista (BDI ≥ 17) kärsivää potilasta, jotka tulivat lähetteellä psykiatriseen erikoissairaanhoitoon ja jotka osallistuivat Masennustalkoot II -tutkimukseen (ODS). Alkoholin käytön häiriöiden tunnistamiseen suunniteltua AUDIT-kyselyä käytettiin merkittävistä alkoholinkäytön ongelmista kärsivien potilaiden tunnistamiseen (AUP, AUDIT ≥ 11).

Tutkimuksen II pääanalyyseissä vertailtiin 127:n masennuksesta kärsivän (ilman alkoholinkäyttöongelmaa) potilaan ryhmää (non-AUP) 89:n merkittävistä alkoholinkäyttöongelmista kärsivän masennuspotilaan ryhmään (AUP). Kaikkien potilaiden temperamentti ja luonnepiirteet määritettiin alkutilanteessa ja 6 viikon seuranta-ajan päätteeksi TCI-R kyselyllä. Ryhmien välisten erojen ja toisaalta TCI-R muutoksien (6 viikon seuranta-aikana), sekä masennuksen hoitovasteen (ΔMADRS) välisen yhteyden analysointiin käytettiin tilastollisia GLM-malleja.

Tutkimuksessa III 173:n potilaan masennusoireet (MADRS) ja temperamentti- ja luonnepiirteet (TCI-R) määritettiin 6 viikkoa masennuksen hoidon aloittamisen jälkeen. Masennuksen pitkän aikavälin tulosta (MADRS-pisteet kolmessa seurantapisteessä 6 viikon, 6 kuukauden ja 24 kuukauden kuluttua) ennustettiin tilastollisella linear mixed effects -mallilla, jossa selittävinä muuttujina käytettiin potilasryhmää (AUP tai non-AUP), sukupuolta, sekä AUP x sukupuoli ja AUP x aika -vuorovaikutusmuuttujia yhdessä temperamentti- ja luonnepiirre ulottuvuuksien kanssa.

Tutkimuksessa IV 204 potilaan temperamentti (TCI-R) ja psykiatriset diagnoosit (Mini International neuropsykiatrinen haastattelu, MINI) määritettiin tulovaiheessa. Potilaiden temperamenttiprofiiliklusterien määrittelemisessä käytettiin tilastollista klusterianalyysiä ja tilastollista logistista regressioanalyysiä käytettiin erilaisten ahdistuneisuushäiriöiden ennustamiseen käyttäen eri temperamenttiprofiiliklustereita selittävinä muuttujina.

Tulokset. Tutkimuksessa I löydettiin yhteys vinoutuneen temperamenttiprofiilin (poikkeamat yleisväestön keskiarvosta eri temperamentti ulottuvuuksissa) ja vakavan masennuksen (MDD) oirekuvan vakavuuden välillä, mutta temperamenttiprofiilit eivät itsenäisesti ennustaneet masennuslääkkeen vastetta merkittävästi. Alkutilanteessa vaikeimmista masennusoireista kärsivät potilaat saivat vähäisimmän vasteen masennuslääkkeelle. Tilastollinen GLM-malli, jossa käytettiin selittävinä muuttujina alkutilanteessa määritettyä masennuksen vegetatiivista oirekomponenttia, ikää ja temperamenttiprofiiliklustereita, selitti 20% lopputilanteen MADRS-pistemäärän varianssista.

Toisessa osatutkimuksessa alkoholin käytön ongelmat (AUP) ennustivat tilastollisesti merkitsevästi Elämyshakuisuus (Novelty Seeking), Itseohjautuvuus (Self-Directedness) ja Sinnikkyys (Persistence) ominaisuuksien varianssia GLM-malleissa. Hyväksynnän hakeminen (Reward Dependence) ominaisuuden muutos 6 viikon seuranta-aikana selitti 14% masennuksen hoitovasteesta (ΔMADRS) alkoholin ongelmakäyttäjillä (AUP), mutta vastaava selitysmalli ei ollut merkitsevä hoitovasteen ennustamisessa vähäisemmän alkoholin käytön potilasryhmässä (non-AUP). Itseohjautuvuus ja Henkisyys (Self-Transcendence) luonnepiirreominaisuuksien muutokset selittivät yhteensä 13% hoitovasteen (ΔMADRS) vaihtelusta non-AUP potilasryhmässä, mutta kaikki luonnepiirreominaisuudet olivat ei-merkitseviä hoitovasteen ennustamisessa AUP ryhmän potilailla. Alkoholin ongelmakäyttäjien potilasryhmällä oli alhaisempi Itseohjautuvuus ja Sinnikkyys, sekä korkeampi Elämyshakuisuus verrattuna potilaisiin, joilla ei ollut alkoholin ongelmakäyttöä.

Tutkimuksessa III huonompaa masennuksen pitkän aikavälin hoitotulosta (MADRS-pisteet 6 viikkoa, 6 kuukautta ja 24 kuukautta) ennusti AUP × aika -vuorovaikutusmuuttuja ($p<0,001$) yhdessä matalan Hyväksynnän hakeminen ominaisuuden kanssa ($p=0,003$). Sukupuoli ja kaikki muut temperamentti- ja luonnepiirre ominaisuudet olivat ei-merkitseviä masennuksen pitkän aikavälin hoitotuloksen selittäjinä, kun näiden yhteyksiä analysoitiin lineaarisessa sekamallissa (linear mixed effects model).

Tutkimuksessa IV temperamenttiprofiilit jakautuivat neljään eri klusteriin 1) Elämyshakuiset, joilla oli korkeimmat Elämyshakuisuus-pistemäärät (n=56), 2) Sinnikkäät, joilla oli korkeimmat Sinnikkyys-pistemäärät (n=36), 3) Varautuneet, joilla oli alimmat Elämyshakuisuus-pistemäärät (n=66) ja 4) Uupuneet, joilla oli korkeimmat Vaikeuksien välttämis- (Harm Avoidance), alimmat Hyväksynnän hakemis- ja alimmat Sinnikkyys-pistemäärät (n=58). Kun mahdollisten sekoittavien muuttujien vaikutukset kontrolloitiin logistisissa regressiomalleissa Elämyshakuiset-temperamenttiprofiili ennusti paniikkihäiriötä ja/tai julkisten paikkojen pelkoa vedonlyöntikertoimella [OR]=3,5 (95%:n luottamusväli [CI]=1,8-6,9, $p<0,001$), Uupuneet ennusti sosiaalisten tilanteiden pelkoa [OR]=3,4 (95% [CI]=1,6−7,5, $p=0,002$) ja Varautuneet ennusti yleistynyttä ahdistuneisuushäiriötä [OR]=2,6 (95% [CI]=1,2−5,3, $p=0,01$).

Johtopäätökset. Temperamenttiprofiilit olivat yhteydessä sekä masennuksen vakavuuteen, että masennuksen lääkehoitovasteeseen. Pelkän temperamenttiprofiilin vaikutus oli vähäinen, mutta yhdessä masennuksen vegetatiivisen oirekomponentin

kanssa niiden selittävä voima oli suurempi, viitaten näiden kahden tekijän yhteyteen masennuksen biologisessa taustassa. (I)

Havaitut muutokset (6 viikon seuranta-aikana) Hyväksynnän hakeminen -temperamenttiominaisuudessa ja matalampi Itseohjautuvuus -luonnepiirreominaisuus alkoholin ongelmakäytöstä kärsivillä potilailla voivat heijastaa tämän potilasryhmän muista poikkeavia masennuksen biologisia taustatekijöitä. Luonteenpiirreominaisuuksien muutokset näyttävät sen sijaan olevan yhteydessä masennuksen akuuttiin hoitovasteeseen masennuspotilailla, joilla ei ole merkittävää alkoholin riskikäyttöä. (II)

Alkoholin ongelmakäyttö vaikutti mahdollisesti siihen, että korkea Hyväksynnän hakeminen -temperamentti ominaisuus oli yhteydessä parempaan masennuksen hoitovasteen kehitykseen kahden vuoden seuranta-aikana. Kun alkoholin käytön vaikutus otettiin huomioon, Vaikeuksien välttäminen ja Itseohjautuvuus eivät ennustaneet masennuksen hoitovasteen kehitystä merkitsevästi kahden vuoden seurannassa. (III)

Elämyshakuiset-temperamenttiprofiili oli yhteydessä paniikkihäiriöön, Varautuneet yleistyneeseen ahdistuneisuushäiriöön, Uupuneet sosiaalisten tilanteiden pelkoon ja Sinnikkäät matalampaan kaikkien ahdistuneisuushäiriöiden riskiin. Tämä tulos viittaa siihen, että TCI-R voisi tarjota mittamenetelmän ennustamaan ahdistuneisuushäiriöiden kehittymisen riskiä masennuspotilailla. (IV)

TABLE OF CONTENTS

ABBREVIATIONS

AA = Alcohol Abuse

ACC = Anterior Cingulate Cyrus

AD = Alcohol Dependence

AUD = Alcohol Use Disorder

AUDIT = Alcohol Use Disorders Identification Test

AUP = Alcohol Use Problems

BA = Behavioral Activation Therapy

BBB = Blood Brain Barrier

BDI = Beck Depression Inventory

CNS = Central Nervous System

C = Cooperativeness

CRH = Corticotropin Releasing Hormone

CSF = Cerebrospinal Fluid

DALY = Disability Adjusted Life Years

DBS = Deep Brain Stimulation

DEPGEN = Pharmacogenetic Study on Depression

dlPFC = Dorsolateral Prefrontal Cortex

DSM-III = Diagnostic and Statistics Manual of mental disorders (3rd edition)

DSM-IV = Diagnostic and Statistics Manual of mental disorders (4th edition)

DSM-5 = Diagnostic and Statistics Manual of mental disorders (5th edition)

DTI = Diffusion Tensor Imaging

ECT = Electroconvulsive Therapy

FFM = Five Factor Model of personality

GABA = Gamma Amino Butyric Acid

GAD = Generalized Anxiety Disorder

GHQ = General Health Questionnaire

GLM = General Linear Model

GWAS = Genome-Wide Association Study

GxE = Gene x Environment interaction

HAM-D = Hamilton Rating Scale for Depression

HPA = Hypothalamic-Pituitary-Adrenal

LOCF = Last Observation Carried Forward

HA = Harm Avoidance

ICD-10 =International Classification of Diseases 10th revision

ICD-11 =International Classification of Diseases 11th revision

IDO = Indoleamine 2,3-dioxygenase

IL-1 = Interleukin-1

IL-6 = Interleukin-6

IL-10 = Interleukin-10

IL-18 = Interleukin-18

MADRS = Montgomery-Åsberg Depression Rating Scale

MDD = Major Depressive Disorder

MDE = Major Depressive Episode

MI = Motivational Interviewing

MINI = Mini International Neuropsychiatric Interview 5.0

MRI = Magnetic Resonance Imaging

MRS = Magnetic Resonance Spectroscopy

NEO-PI-R = NEO-Personality Inventory Revised

NS = Novelty Seeking

ODS = Ostrobothnia Depression Study

omega-3-FA = Omega-3-Fatty Acid

P = Persistence

pCASL = Pseudo-Continuous Arterial Spin Labeling

PD = Panic Disorder

PDA = Panic Disorder and/or Agoraphobia

PET = Positron Emission Tomography

RD = Reward Dependency

rTMS = Repetitive Transcranial Magnetic Stimulation

SAD = Social Anxiety Disorder

SCL-90 = Symptom Checklist-90

SD = Self-Directedness

SNP = Single Nucleotide Polymorphism

SNRI = Serotonin and Noradrenaline Reuptake Inhibitor

SP = Social Phobia

SPECT = Single Photon Emission Computed Tomography

SSRI = Selective Serotonin Reuptake Inhibitor

ST = Self-Transcendence

SUD = Substance Use Disorder

T3 = Triiodothyronin

TCI = Temperament and Character Inventory

TCI-R = Temperament and Character Inventory – Revised

tDCS = Transcranial Direct Current Stimulation

TNF = Tumor Necrosis Factor

TPQ = Tridimensional Personality Questionnaire

VNS = Vagal Nerve Stimulation

YLD = Years Lived with Disability

YLL = Years of Life Lost

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to throughout the text by Roman numerals I-IV:

I PAAVONEN, V., KAMPMAN, O., ILLI, A., VIIKKI, M., SETALA-SOIKKELI, E. and LEINONEN, E., 2014. A cluster model of temperament as an indicator of antidepressant response and symptom severity in major depression. Psychiatry Investigation, 11(1), pp. 18-23.

II PAAVONEN, V., LUOTO, K., KOIVUKANGAS, A., LASSILA, A., LEINONEN, E. and KAMPMAN, O., 2016. Temperament and character profiles associated with depression and treatment response in patients with or without comorbid substance abuse. Psychiatry Research, 245, pp. 250-258.

III PAAVONEN, V., LUOTO, K., LASSILA, A., LEINONEN, E. and KAMPMAN, O., 2018a. Temperament and character profiles are associated with depression outcome in psychiatric secondary care patients with harmful drinking. Comprehensive Psychiatry, 84, pp. 26-31.

IV PAAVONEN, V., LUOTO, K., LASSILA, A., LEINONEN, E. and KAMPMAN, O., 2018b. Temperament clusters associate with anxiety disorder comorbidity in depression. Journal of Affective Disorders, 236, pp. 252-258.

1 INTRODUCTION

Depressive disorders have been a growing public health concern in Finland during the 21th century and the annual prevalence for these disorders is approximately ten percent in the Finnish population (Markkula, Suvisaari et al. 2015). This growth in prevalence could be a global concern and the point prevalence of major depressive disorder (MDD) has been on average 5% in developed western countries (Ferrari, Somerville et al. 2013). Depressive disorders are a leading cause of global burden of disease (Wittchen, Jacobi et al. 2011) and are associated with low quality of life, sick leaves and high suicide risk (Alonso, Angermeyer et al. 2004, Alonso, Petukhova et al. 2011, Ösby, Brandt et al. 2001). Contributing to the burden of disease, the recurrence of depressive episodes could be associated with half of the cases and the duration of single episode is on average 6 months (Burcusa, Iacono 2007, Lewinsohn, Clarke et al. 1994). Depressive disorders are syndromes consisting of combinations of dysphoric, retardation and vegetative symptoms and different symptoms seem to be associated with different outcomes of depression (Suzuki, Aoshima et al. 2005, Okazaki, Tominaga et al. 2010, Kamata, Suzuki et al. 2011, Higuchi, Sato et al. 2008a). Alcohol consumption posits detrimental effects on vast number of diseases (Rehm, Gmel et al. 2017) and substance use problems, especially alcohol use, are another major public health and economic concern in European countries, including Finland (Barrio, Reynolds et al. 2017). Up to one fourth of patients with MDD suffer from concurrent alcohol use disorder (AUD) which can have a detrimental effect on recovery from depressive episodes and lead to more chronic disease courses (Davis, Uezato et al. 2008, Melartin, Rytsala et al. 2002, Melartin, Mantere et al. 2014, Burcusa, Iacono 2007, Holzel, Harter et al. 2011). These patients with concurrent mental illness and AUD are diagnosed with "dual diagnosis" and in spite of promising treatment options for these patients, more thorough research is needed on the possible predefined moderators and mediators of treatment outcome in this patient group (Riper, Andersson et al. 2014).

Dimensional assessment of the human personality has been used in scientific studies and the new versions of the Diagnostic and Statistics Manual of mental disorders (DSM-5) and International Classification of Diseases (ICD-11) have

dimensional diagnostics algorithms for personality disorders (Bach, Sellbom et al. 2018). According to Robert Cloninger's biopsychological model, the human personality is composed of temperament and character (Cloninger, Svrakic et al. 1993). Temperament is the more stable core of the personality resulting in individual reactions to different life-events whereas character is essential, for example, in determining social performance (Cloninger, Svrakic et al. 1993). Temperament and character traits are associated with depressive disorders, outcome of depression, alcohol use and anxiety disorders (Kampman, Poutanen 2011, Balestri, Porcelli et al. 2019, Miettunen, Raevuori 2012, Howard, Kivlahan et al. 1997, Foulds, Mulder et al. 2016). Alcohol use problems could modulate the association between temperament and character and depression outcome and better knowledge of this effect could help in developing more effective treatments for dual diagnosis patients. Better knowledge of the associations between temperament and anxiety disorders could also aid in the improvement of treatments for comorbid depression, because the comorbidity of anxiety disorders also has detrimental effects on recovery from depression (Holzel, Harter et al. 2011).

This thesis consists of prospective clinical cohort studies predicting short-term, mid-term and long-term outcomes of depression with temperament (and character) profiles or short-term changes in temperament or character. The possible modulating effect of alcohol use problems or vegetative symptoms of depression on those associations are studied. The cross-sectional part of the study analyses the relationship between temperament profile and different anxiety disorder comorbidities in depressed patients. Moreover, the unique temperament and character characteristics of depressed patients with alcohol use problems are examined.

2 REVIEW OF THE LITERATURE

2.1 Depression as a dimensional concept

Depression is a common word in everyday language. However, its meanings vary considerably according to the context in which it is referred to. For example, it is commonly used to describe a current negative mood state after an adverse life event or in more casual situations, but in psychiatric clinics depression often refers to a severe illness with low level of functioning and high risk of suicide (Ösby, Brandt et al. 2001, Alonso, Petukhova et al. 2011).

As a clinical disorder depression is composed of a combination of different symptoms which affect mood state, ability to experience pleasure, cognitive and somatic functions and which negatively bias self-evaluation or cause suicidal ideation. These symptoms causing extensive and varied perturbations in patients are deemed existent or non-existent and the severity of the disorder is mainly evaluated in terms of how many different symptoms it causes. Another criterion for depressive disorders is persistence of these symptoms over a specific period of time. In this respect depressive disorders are defined through two non-quantitative aspects, one concerning the number of extant symptoms and the other concerning their duration, whereas the severity of symptoms is only taken slightly into account in severe cases. (American Psychiatric Association 2013, WHO | International Classification of Diseases, 11th Revision (ICD-11), World Health Organization 1992) This can be considered as weakness in clinical practice, because it is widely acknowledged that the course of depression is more linearly associated with the severity of depressive symptoms (van Beljouw, Verhaak et al. 2010). Moreover, patients with subclinical depressive symptoms might go unnoticed in the non-quantitative assessment of depressive disorders even though they may constitute a clinically relevant population in need of treatment (Peters, Shankman et al. 2015). These shortcomings of the categorical assessment of depressive disorders may have led to the frequent use of different linear measures of symptoms of depression in evaluating patients and informing clinical decision-making.

2.1.1 Measures of symptoms of depression

There are numerous different rating scales for gathering information on different depressive symptoms, some of which are brief self-report questionnaires used as screening tools while others gather detailed information on different symptoms of depression by interviews conducted by trained professionals. The general screening of different psychopathologies (including depressive symptoms) can be made via self-report questionnaires General Health Questionnaire (GHQ, (Goldberg 1972)) and the Symptom Checklist-90 (SCL-90, (Derogatis, Lipman et al. 1973)). Concentrating on symptoms of depressive disorders, the self-report questionnaire, the Beck Depression Inventory (BDI, (Beck, Steer et al. 1996)) has been widely used in screening patients in the community or in general medical population. Observer-rated depressive symptom scales Hamilton Rating Scale for Depression (HAM-D, (Hamilton 1960)) and the Montgomery-Åsberg Depression Rating Scale (MADRS, (Montgomery, Åsberg 1979)) are more commonly used in evaluating severity of depression or response to treatment in patients in psychiatric secondary care or in research settings.

2.1.1.1 Beck Depression Inventory

The Beck Depression Inventory is a self-report questionnaire that collects information on various depressive symptoms and their severity. The original version was published in 1961 and contained 21 items with statements describing different symptom severities (Beck, Ward et al. 1961). Since then several different versions have been introduced to better respond to the depressive symptomatology of more recent diagnostics manuals or better suited for different applications, and the questionnaire has been validated in multiple different languages including Finnish (Aalto, Elovainio et al. 2012).

The Finnish BDI-1A questionnaire consists of 21 items, each of which contain 4 to 7 different statements corresponding to absent (a score of 0), mild (1), moderate (2) and severe (3) symptoms. These items are related to symptoms of sadness, hopelessness, feelings of failure, anhedonia, guilt, punishment, self-dislike, self-accusation, self-harm, crying, irritability, loss of interest in other people, indecisiveness, impaired self-image and ability to work, problems with sleeping, tiredness, loss of appetite, weight loss/gain, somatic preoccupation and loss of libido. The Finnish interpretation guide suggests 0-9 points as corresponding to a subclinical level of depressive symptoms, 10-16 to mild depression, 17-29 to

moderate depression and 30-60 to severe depression. The internal consistency of the BDI has been high in various studies (mean Cronbach's alpha value of 0.87) and test-retest reliability greater than 0.60 (Beck, Aaron T., Steer et al. 1988). The intercorrelation between the BDI and an interview-based depression severity rating scale, MADRS, has been moderate (r=0.65) (Tamaklo, Schubert et al. 1992).

2.1.1.2 Montgomery-Åsberg Depression Rating Scale

The Montgomery-Åsberg depression rating scale was introduced in 1979 as an instrument sensitive to change in depressive symptoms and has been widely used in studies on depression treatment response (Montgomery, Asberg 1979, Serretti, Chiesa et al. 2009, Cuijpers, Li et al. 2010). It consists of 10 items, each including statements guiding the evaluation of symptom severity and evaluated on an ordinal scale from absent to severe (0 to 6 points) as observed in an interview. This interview is conducted by a trained professional and includes one item that represents the interviewer's subjective estimation of the level of the patient's depressive mood. Other items include symptomatology reflecting the patient's own subjective feeling of depressed mood, feelings of anxiety, reduced sleep and appetite, concentration difficulties, reduced initiative ability, anhedonia, pessimistic thoughts and suicidal ideation. The guidelines suggest interpretating 0-7 points as no depression, 8-14 points as depressive symptoms, 15-24 points as mild depression, 25-30 points as moderate depression, 31-43 points as severe depression and 44 or more points as very severe depression (Montgomery, Åsberg 1979). MADRS has shown acceptable construct validity and test-retest reliability (r=0.76) (Davidson, Turnbull et al. 1986), but some items (i.e. suicidal thoughts, sleep disturbance and reduced appetite) have been poorly correlated with the remainder of the scale and several factor analyses have suggested more than one factor for MADRS (Suzuki, Aoshima et al. 2005).

2.1.2 Symptoms of depression

As is evident in the specifications of different symptom modalities of the BDI and MADRS described above, depressive symptoms have a deleterious effect on individual well-being on multiple different levels i.e. cognitive, affective, behavioral, somatic and vegetative (Kanter, Busch et al. 2008). The associations between these different symptoms and depressive states were originally found through observations and interviewing depressed patients (Paykel 2008). The criteria

including the core symptoms for different clinical depressive disorders in the diagnostics manuals (DSM and ICD) are defined by committee agreement based on empirical research data (Paykel 2008). The core symptoms of depression are depressed mood and loss of interest or pleasure (American Psychiatric Association 2013), and fatigability or loss of energy (World Health Organization 1992). Although the other possible symptoms of depression are various, studies have supported the unidimensional structure of the symptoms of major depressive disorder (Aggen, Neale et al. 2005) and the wide variety of symptoms included in the BDI (Beck, Steer et al. 1988). However, three orthogonal genetic factors have been suggested to underlie MDD, one of which has been associated with vegetative symptoms of depression (Kendler, Aggen et al. 2013). Different subtypes of depressive disorders (depression with atypical or melancholic features or seasonal pattern) with differences in vegetative symptoms have traditionally been recognized (DSM and ICD) (Paykel 2008).

2.1.2.1 Vegetative symptoms of depression

Vegetative symptoms of depression refer to symptoms such as increased or decreased appetite, weight gain or loss of weight and insomnia or hypersomnia (Grimaldi, Partonen et al. 2009). Historically these vegetative symptoms (i.e. decreased appetite and insomnia) have been associated with a more "endogenous" type of depression defined as being less associated with life-stressors (Paykel 2008). Atypical vegetative symptoms (increased appetite and hypersomnia) have been associated with the early stages of a depressive episode in patients with seasonal affective disorder and seasonal changes in the vegetative functions have been suggested to predispose to seasonal pattern of depressive symptomatology (Grimaldi, Partonen et al. 2009). Vegetative symptoms seem to be associated with elevated levels of acute phase protein haptoglobin and immunological mediators such as IL-6 and IL-1 (Maes 1993), and predict the emergence of cognitive symptoms of depression in patients treated with proinflammatory cytokines (Wichers, Koek et al. 2005). Low grade inflammation is common in patients with depression (Osimo, Baxter et al. 2019) and it is associated with the vegetative symptoms, perhaps more specifically with sleep problems and energy level (Jokela, Virtanen et al. 2016, Fried, von Stockert et al. 2019).

A three-factor model for MADRS in MDD has been proposed with a vegetative symptom factor consisting of symptoms of reduced sleep and appetite and inner tension (Suzuki, Aoshima et al. 2005). These vegetative symptoms have had delayed

response to electroconvulsive therapy (ECT) (Okazaki, Tominaga et al. 2010) and high scores in the vegetative factor have been associated with A allele of serotonin receptor 5HT2A (Kamata, Suzuki et al. 2011). Moreover, high scores on the vegetative factor have also been associated with poorer outcome of fluvoxamine treatment (Higuchi, Sato et al. 2008a), and have been suggested to be indifferent in predicting response to other antidepressant milnacipran (Higuchi, Sato et al. 2008b) in Japanese depressed patients.

2.2 Major depressive disorder (MDD)

Major depressive disorder first appeared in the official disease classification in 1980 when the DSM-III was published (American Psychiatric Association 1980). This classification of depression was to be used to make a distinction between bipolar disorder and less severe dysthymia. After the publication of the DSM-III, the definition of MDD has gone through only minor changes (American Psychiatric Association 2013). The diagnostic criteria for depressive episodes and recurrent depressive disorder episodes in the International Classification of Diseases (ICD-10) are mainly similar to the DSM criteria for MDD. However, the criteria in the ICD-10 include fatigue or loss of energy as one possible core criterion and require one less symptom for the diagnosis (World Health Organization 1992, American Psychiatric Association 2013). In Finland the ICD-10 is still used for diagnosing patients in clinical settings, but in research settings the use of the DSM is the gold standard. In this thesis depressive episodes or recurrent depression according to ICD-10 criteria are only referred to if specifically noted.

2.2.1 Diagnosis of MDD

There are five diagnostic criteria for MDD in the DSM-5. The first (I) requirement for the diagnosis is presence of five or more depressive symptoms over for at least 2-week time periods and these symptoms are required to represent a change from previous functioning. One of the core symptoms of either 1) depressed mood or 2) loss of interest or pleasure must be present in addition to other possible symptoms: 3) significant weight loss or weight gain, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or guilt, 8) diminished ability to think or concentrate or indecisiveness,

9) recurrent thoughts of death or suicide attempt. The second (II) diagnostic criteria include clinically significant distress or impairment in social or other areas of functioning. Third (III) the criteria to be met for a diagnosis of major depressive episode (MDE) include exclusion of substance abuse or depression induced by a medical condition. The two other criteria for MDD also concern exclusion of other disorders: (IV) depressive episode is not better explained by schizophrenia or other disorders in that spectrum, and (V) the patient has never had a manic or hypomanic episode. (American Psychiatric Association 2013)

The possible depressive symptoms in diagnosing MDD have remained unchanged, but some other minor alterations to the diagnostic criteria exist between different versions of the DSM. The most notable and controversial change made to the DSM-5 was the removal of bereavement exclusion criteria, which may be associated with a minor increase in the prevalence of this disorder (Clesse, Leray et al. 2017).

2.2.2 Epidemiology of MDD

Studies on the prevalence of depression are sensitive to discrepancies in study design and methodology and studies using symptom scales as measures of depression result in markedly higher prevalence whereas there is no significant difference in prevalence according to the use of ICD or DSM criteria (Ferrari, Somerville et al. 2013). A meta-analysis estimated the point prevalence of major depression in Western Europe to be 4.7%, which is also the global average (Ferrari, Somerville et al. 2013). Developing countries have mainly higher prevalence of MDD with the exception of a slightly lower prevalence of 4.0% found in East/Southeast Asia (Ferrari, Somerville et al. 2013). Depression is twice as common in females as in men (Culbertson 1997) and a higher prevalence is found in adults of working age compared to other age groups (Ferrari, Somerville et al. 2013).

Disability adjusted life years (DALYs) are a standard measure for estimating the burden of disease. This is the sum of life years lost (YLL) due to premature mortality and years of life lived with a disability (YLD) (Murray, Lopez (editors) 1996). Even though no disorder specific YLL could be estimated for depression, it was the leading cause of YLD in the global burden of disease study in 2000 and was estimated as the third leading cause of global disease burden (equivalent to 4.3% of DALYs) (WHO | The global burden of disease: 2004 update 2008, Global Burden of Disease 2000: version 2 methods and results. Available:

http://www.who.int/healthinfo/paper50.pdf. 2002). MDD and dysthymia were studied as separate diseases and population surveys were conducted to determine the disease weights used in calculating YLDs in The Burden of Disease Study 2010 (Ferrari, Charlson et al. 2013). In that study MDD was the second leading cause of YLDs (accounting for 8.2% of global YLDs) and accounted for 2.5% of global DALYs (Ferrari, Charlson et al. 2013). MDD also explained part of the DALYs associated with ischemic heart disease and suicide as it was considered a risk factor for them (Ferrari, Charlson et al. 2013). The overall global DALYs accounting for depression in the study was 3.8% and 85% of the burden was attributable to MDD (and 15% to dysthymia) (Ferrari, Charlson et al. 2013).

The annual prevalence of 6.5% of depressive disorders in Finnish population was comparable to those in other industrialized western countries in the Health 2000 study (Pirkola, Isometsa et al. 2005). In the follow-up Finnish Health 2011 Survey MDD had a higher prevalence at 7.4% and the prevalence of dysthymia was 4.5% (Markkula, Suvisaari et al. 2015).

2.2.3 Etiology of MDD

2.2.3.1 Risk factors and an integrative model for predicting depression

Major depressive disorder is a multifaceted syndrome associated with symptoms of emotional, cognitive or neurovegetative functions and psychomotor activity (Fava, Kendler 2000). The various environmental and individual risk factors for depression consist of female gender (Culbertson 1997), genetic influences (Flint, Kendler 2014), adverse experiences in childhood (Parker 1979, Holmes, Robins 1988, Tennant 1988, Maniglio 2010), specific personality related factors (Boyce, Parker et al. 1991, Kampman, Poutanen 2011), stressful life-events (Kessler 1997), low social support and marital difficulties (Patten, Williams et al. 2010, Whisman, Sheldon et al. 2000), and prior history of depression or anxiety (Harrington, Fudge et al. 1990, Breslau, Schultz et al. 1995).

Kendler et al., used structural equation modelling to generate a developmental model for the etiology of MDD separately for men and women (Kendler, Gardner et al. 2002, Kendler, Gardner et al. 2006). These models included eighteen risk factors considered in five tiers: 1) childhood (genetic risk, disturbed family environment, childhood sexual abuse, and childhood parental loss), 2) early adolescence (neuroticism, self-esteem and early onset anxiety, and conduct disorder),

3) late adolescence (educational attainment, lifetime trauma, social support, and substance abuse), 4) adulthood (history of divorce and past history of depression), 5) the previous year (marital problems, difficulties, and stressful life-events). The best fitting models using multiple correlations and paths were relatively similar for men and women and were able to explain half of the variance in depressive episode incidence in the previous year in both genders. These findings were concluded as reflecting the etiological complexity of MDD and suggested to indicate a mainly similar etiology of MDD for both genders. (Kendler, Gardner et al. 2002, Kendler, Gardner et al. 2006)

2.2.3.2 Neuroimaging findings

Magnetic resonance imaging (MRI) (Caetano, Hatch et al. 2004) and its more recent applications fMRI (Ogava, et al. 1993) and diffusion tensor imaging (DTI) (Peng Fang, Ling-Li Zeng et al. 2012) are the most widely used methods in imaging changes in the structure or functionality of the central nervous system (CNS) in MDD patients because of their high resolution and lack of radiation exposure. Other imaging methods include magnetic resonance spectroscopy (MRS) (Brambilla, Stanley et al. 2002), positron emission tomography (PET) (Alavi, et al. 1986), single photon emission computed tomography (SPECT) (Bhardwaj, Chakrabarti et al. 2010), and the more recently introduced pseudo-continuous arterial spin labelling (pCASL) (Fazlollahi, Bourgeat et al. 2015). These methods are used in imaging biochemical, hemodynamic and pharmacokinetic events in vivo. The structural changes in the CNS of MDD patients include increased volume of lateral ventricles and cerebrospinal fluid (CSF), increased rate of hyperintensities of subcortical gray matter, and smaller volumes of basal ganglia, thalamus, hippocampus, frontal lobes in multiple locations including orbitofrontal cortex and gyrus rectus (Kempton, Salvador et al. 2011). However, according to a meta-analysis (Kempton, Salvador et al. 2011) there seem to be no alterations in amygdala volumes in depression. Functional changes associated with depressive states are described in chapters 2.2.4., 2.2.4.1, and 2.2.4.2.

2.2.3.3 Heritability and genetic findings

The estimate for the heritability of MDD has been 37% according to twin studies (Sullivan, Neale et al. 2000) in spite of claims of heritability as high as 78%

(McGuffin, Katz et al. 1996). Genome-wide studies of depression have shown heritability rates for depression of 21 to 32% (Direk, Williams et al. 2017, Lubke 2012). Females seem to have higher heritability of MDD (42%) than males (29%) (Kendler, Gatz et al. 2006) suggesting different genetic backgrounds for the two sexes (Flint, Kendler 2014).

Traditional genetic studies have been hypothesis-based and searched for candidate genes in predicting depression and meta-analyses of these studies have yielded significant associations between 7 different gene variants and depression: 5HTTP/SLC6A4, APOE, DRD4, GNB3, HTR1A, MTHFR, and SLC6A3 (Flint, Kendler 2014). However, these associations have not been replicated in genome-wide association studies (GWASs) with large numbers of subjects (Flint, Kendler 2014). In addition to findings in candidate gene studies, some new single nucleotide polymorphisms (SNPs) such as rs9825823, rs1863918, rs12415800 and rs35936514 have reportedly been associated with depression symptomatology in the GWASs (Direk, Williams et al. 2017, Matsunami, Nishida et al. 2016, Cai, Bigdeli et al. 2015). It has been suggested that there are most likely a large number of different genetic variants with small effect sizes conferring susceptibility to depression although the possibility of rare variants with greater effect size is not ruled out. Nevertheless, the findings in GWAS have also been hard to replicate and it has been argued that even larger sample sizes (of over n=50,000) would be needed to show significant results in the search for the genetic background of MDD (Flint, Kendler 2014). Indeed, a recent GWAS analyzing two samples with over 70,000 subjects was able to replicate an association between broad depression phenotype and SNP located in an intron of the FHIT gene (Direk, Williams et al. 2017). Other possible methods suggested to obtain significant results include studying narrower subtypes of depression or more specific phenotypes associated with depression (Flint, Kendler 2014). Different genetic susceptibilities could also be associated with different aspects of depressive symptomatology as three differential genetic factors have been suggested to exist specifically reflecting the psychomotor/cognitive, mood, and neurovegetative features of MDD (Kendler, Aggen et al. 2013).

2.2.3.4 Psychological theories

The traditional cognitive model of depression (Beck 1967) proposes that depressed individuals have maladaptive schemas consisting of feelings of worthlessness, hopelessness and rejection. This causes negatively biased appraisal of life events leading again to reinforcement of these negative schemas and the maintenance of

depressive state. Disrupted cognitive functions include: 1) arbitrary judgement, 2) selective abstracting, 3) overgeneralization, 4) over/undervaluation, 5) personalization and 6) splitting.

Behavioral theory emphasizes the role of avoidance as a central causal factor in the etiological process of depression (Kanter, Busch et al. 2008, Carvalho, Hopko 2011). Some theorists consider behavior as a wide concept including verbal behavior (also in the form of thought) as behavior of framing events rationally (Barnes-Holmes, Hayes et al. 2001). Behavioral studies have also considered avoidance in a wide sense including 1) cognitive aspects of avoidance such as denying, minimizing, ruminating or passive "submission" to the current state of affairs as well as 2) behavioral avoidance in terms of participation in alternative activities. This behavioral avoidance may also include substance abuse, gambling, binge eating, or overexpression of negative emotions (e.g. shouting at others) (Carvalho, Hopko 2011). According to the behavioral theory of depression, avoidance leads to depressive state via absence of reinforcement and reward caused by this passivity or withdrawal (Carvalho, Hopko 2011).

The early psychological theories including psychodynamic theory are based on the works of Sigmund Freud. Although similarities across behavioral and psychodynamic theories have been suggested, the psychodynamic object loss model of depression has not attracted scientific interest in recent decades (Akiskal, McKinney 1973, Wilkins 1971).

2.2.4 Pathogenesis of MDD

The pathogenesis of depression is not completely understood. Although malfunctions in monoaminergic (serotonin, norepinephrine and dopaminergic) metabolism are associated with depression, the monoamine theory of depression developed in the 1950s and 60s is inadequate in explaining the pathogenesis of depression (Caldecott-Hazard, Morgan et al. 1991). Impaired corticosteroid signaling associated with increased production of corticotropin-releasing hormone (CRH) in CNS was considered an epiphenomenon of depression during 20th century but more recently has been proposed as a causal factor in the pathogenesis of depression (Holsboer 2000).

2.2.4.1 Newer hypotheses explaining the pathogenesis of depression

Because no comprehensive explanation has been found, many hypotheses have recently been proposed to explain the phenomenology and pathogenesis of depression. These include disrupted neurogenesis in the hippocampus (Samuels, Hen 2011), fibroblast growth factor (FGF) associated neuroplasticity (Turner, Watson et al. 2012), GABAergic deficit (Luscher, Shen et al. 2011), nitrosative stress (Anderson, Berk et al. 2014), and immune-kynurenine pathway (Won, Kim 2016, Allison, Ditor 2014) as hypotheses for the pathogenesis of depression. These hypotheses are not exclusive of one another and disrupted neurogenesis can even be considered to be an extension of the theory of impaired corticosteroid signaling, whereas GABAergic functions could be associated with neurogenesis in the hippocampus (Holsboer 2000, Samuels, Hen 2011, Luscher, Shen et al. 2011).

The findings supporting the hypotheses in preceding paragraph suggest chronic stress induced inflammatory state disrupting the neurogenesis and causing a neurotoxic effect on glial cells in the CNS leading to depressive state (Allison, Ditor 2014, Won, Kim 2016, Holsboer 2000, Samuels, Hen 2011). The chronic stress could be induced via epigenetic regulation of the expression of glucocorticoid receptor in individuals with childhood abuse, leading to altered functions on the hypothalamic-pituitary-adrenal (HPA) axis and resulting in chronically high level of cortisol associated with stress (McGowan, Sasaki et al. 2009, Holsboer 2000). Chronic high stress levels could result in higher expression of pro-inflammatory cytokines such as tumor necrosis factor (TNF), IL-1, IL-6 and IL-18 (Bertini, Garattini et al. 1993, Spengler, Chensue et al. 1994, Borovikova, Ivanova et al. 2000) and downregulation of anti-inflammatory IL-10 (Borovikova, Ivanova et al. 2000) via complex mechanisms and biochemical cascades (Pavlov, Tracey 2005, Haskó, Szabó 1998). Higher levels of pro-inflammatory cytokines IL-1, IL-6 and TNF are associated with cognitive and emotional symptoms (Reichenberg, Yirmiya et al. 2001, Strike, Wardle et al. 2004, Wright, Strike et al. 2005) and high levels of TNF and IL-6 and low level of anti-inflammatory IL-10 are found in MDD patients (Müller 2014, Kim, Na et al. 2007, Dhabhar, Burke et al. 2009).

The immune-kynurenine pathway hypothesis regarding the etiology of depression is supported by findings that demonstrate how higher concentrations of cytokines such as TNF result in enhanced activity of indoleamine 2,3-dioxygenase (IDO) enzyme (Robinson, Hale et al. 2005, Heyes, Achim et al. 1996). Increased activity of this enzyme may lead to increased level of extrahepatic metabolism of tryptophan to kynurenine (Won, Kim 2016). The extrahepatic kynurenine and one

of its metabolites, 3-hydroxykynurenine, penetrate the blood brain barrier (BBB) causing elevation in these molecules in the CNS (Won, Kim 2016). Whereas 3-hydroxykynurenine may have neurotoxic effects per se, according to the hypothesis inflammatory state in CNS results in increased metabolism of kynurenine in microglia and macrophages by kynurenine mono-oxygenase enzyme resulting in an increase in another neurotoxic metabolite quinolinic acid (Won, Kim 2016, Heyes, Achim et al. 1996, Mellor, Munn 1999). Moreover, increased activity in the metabolic route described shifts the balance away from the other possible metabolic route of kynurenine by kynurenine amino-transferase in astrocytes, resulting in decreased production of kynurenic acid, a metabolite with potential neuroprotective effects (Won, Kim 2016). The resulting imbalance of neurotoxic and neuroprotective metabolites in the CNS is hypothetically linked to progressive degradation of glial and neuronal networks in the CNS leading to the development of depression in conditions of chronic stress (Won, Kim 2016). However, it is noteworthy that these effects are not likely pathognomonic to depression, and thus the development of medical agents affecting this system could facilitate the progress of developing novel treatments for various neurodegradative diseases (Jacobs, Castellano-Gonzalez et al. 2017). Figure 1 illustrates the immune-kynurenine pathway theory.

Gene x Environment (GxE) interactions could be also associated with the effect of serotonin transporter gene variant (5-HTTLPR) and brain derived neurotrophic factor (BDNF) in the pathogenesis of depression by causing impaired serotonin metabolism and disrupted neurogenesis in the hippocampus in patients with early or recent negative life-events (Brown, Craig et al. 2014, Samuels, Hen 2011). However, the GWASs have so far been unable to lend support to the hypotheses in this chapter, which has even led some researchers to question the GxE effects of the known candidate genes (Van der Auwera, Peyrot et al. 2018, Flint, Kendler 2014).

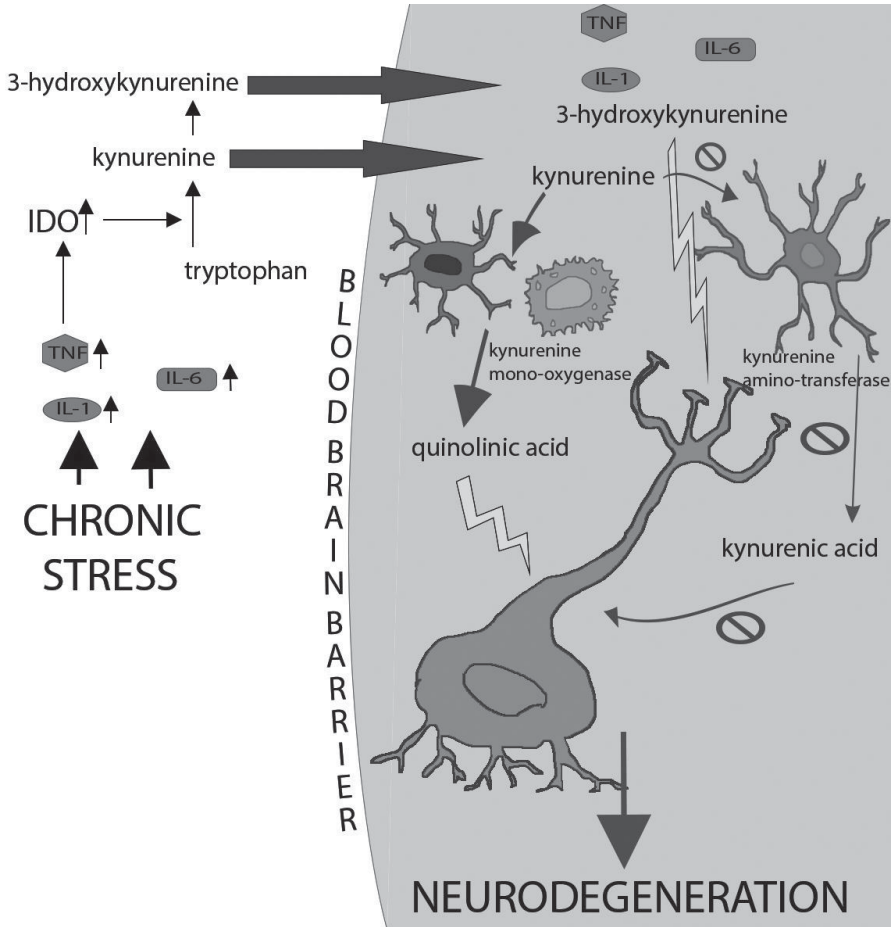

Figure 1 Illustration of immune-kynurenine pathway theory

Abbreviations: TNF = Tumor necrosis factor, IL-1 = Interleukin-1, IL-6 = Interleukin-6, IDO = indoleamine 2,3-dioxygenase

2.2.4.2 Neuroimaging findings on the pathogenesis of depression

The central role of the hippocampus in depressive symptomatology is also supported by findings in MRI studies, which have demonstrated an association between smaller volumes of hippocampus and depression (Kempton, Salvador et al. 2011) as well as poorer outcome of depression at three years and an increase in the volume of the left hippocampus is associated with better antidepressant treatment response (Frodl, Jäger et al. 2008). There seem to be lateral differences in blood perfusion in the brains of depressed patients and the left hemisphere has been shown to be associated with lower perfusion than the right hemisphere (Chen, Bian et al. 2016). It has been

suggested that hypoactivation in left dorsolateral prefrontal cortex (dlPFC) in particular is associated with depressive pathology (Davidson, Pizzagalli et al. 2002). This could explain why rTMS treatment is administered to this particular area, although more recent research has suggested that the treatment effect is likely to be associated with the connectivity of the anterior cingulate cortex (ACC) and the fronto-parietal network (Tik, et al. 2017). Such hypotheses are likely to have shifted the interest in imaging studies to studying the connective tracts between different brain regions. Depressed patients have shown higher connectivity in the fronto-limbic tract (Peng Fang, Ling-Li Zeng et al. 2012) and disrupted connectivity in the uncinate fasciculus (Zhang, Leow et al. 2012) connecting the anterior temporal lobe and inferior areas of the frontal lobe. Studying these connective tracts is interesting because the disrupted white matter could be associated with the neurotoxic effect caused by inflammation as discussed in the preceding chapter.

2.2.4.3 Integration of neuropathological findings of depression with cognitive theories

The accumulating body of functional brain imaging findings in studies with task-related settings has enabled the development of integrative neurocognitive models of psychiatric disorders including depression. These theories aim to better explain the multifaceted clinical phenomenon of depression including its emotional and cognitive symptoms (Disner, Beevers et al. 2011, Malhi, Byrow et al. 2015, Kret, Ploeger 2015). These models have integrated information from a multitude of imaging studies and suggest that impaired brain regions and mechanisms for different cognitive functions are associated with the etiology of depression: rumination, reappraisal, attention control, reward processing, impulsivity and mood lability (Malhi, Byrow et al. 2015). Such integrative theories could arguably lead to a more profound understanding of depression (Disner, Beevers et al. 2011) and by integrating psychological and biological information also aid in finding novel hypotheses for the pathogenesis of depression.

2.3 Comorbidity of MDD

Major depressive disorder has a high rate of comorbidity with other psychiatric and substance use related disorders (Melartin, Rytsälä et al. 2002, Brown, Campbell et al. 2001). These comorbidities are associated with poorer outcome of depression and more difficulties in treatment (Burcusa, Iacono 2007, Holzel, Harter et al. 2011).

2.3.1 Substance use

Substance use is more common among depressed patients than in general population (Sullivan, Fiellin et al. 2005). Harmful substance use can predispose to depression and conversely depression can lead to substance use, for example in an effort to "self-medicate" (Pacek, Martins et al. 2013). The causal relation between substance use and depression is likely complex and possibly reciprocal (Lyons, Schultz et al. 2006, Pacek, Martins et al. 2013).

2.3.1.1 Alcohol use disorders

Alcohol use disorders (AUDs) are the most common substance use related disorders. Whereas DSM-IV divided these disorders into alcohol abuse (AA) and alcohol dependence (AD), in the DSM-5 these disorders have been integrated into a single diagnosis of alcohol use disorder (American Psychiatric Association 1994, American Psychiatric Association 2013). According to the DSM-IV there are two higher order diagnostic criteria that have to be met one year prior to AUD diagnoses: 1) use of alcohol (both AA and AD), and 2) at least one of the four "alcohol abuse criteria" for AA and at least three of the seven "alcohol dependence criteria" for AD (American Psychiatric Association 1994). Under the DSM-5 the second higher order criterion required for AUD demands fulfilling at least two of the eleven "alcohol use disorder criteria" and the severity of this disorder is defined according to how many of these criteria are fulfilled (2 to 3 for mild, 4 to 5 for moderate, and 6 or more for severe) (American Psychiatric Association 2013).

The Alcohol Use Disorder Identification Test (AUDIT) is an instrument designed for identifying alcohol use disorders and high-risk use of alcohol in clinical settings (Bohn, Babor et al. 1995). The cut-off points for different risk levels are suggested to be defined nationally (Babor, Higgins-Biddle et al. 2001) and in Finland scores of over 11 reflect high risk of harm due to alcohol use. AUDIT-C consists of questions 1-3 of AUDIT: How often do you have a drink containing alcohol? How many units of alcohol do you drink on a typical day when you are drinking? How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?, and may also be used as a screening instrument for risk due to alcohol use (Bohn, Babor et al. 1995).

The prevalence of alcohol use disorders in Finnish general population is 4.5% (7.3% in males and 1.4% in females) (Pirkola, Isometsa et al. 2005), whereas in

depressed patients in psychiatric secondary services the prevalence of alcohol use disorder is higher at 25% (Melartin, Rytsala et al. 2002).

The co-occurrence of MDD and alcohol use disorder is called dual diagnosis and is associated with poorer treatment outcome (Agyapong 2013). Alcohol use disorders can lead to impaired response to treatment, more chronic disease courses or recurrence in depressive episodes (Burcusa, Iacono 2007, Holzel, Harter et al. 2011). Depression and Substance Use Disorders (SUDs) seem to have an interactive relation and SUDs also a fluctuating course of symptoms (Agosti, Levin, 2006, Hasin, Liu et al. 2003, Hasin, Tsai et al. 1996). Other factors such as temperament and character traits are associated with the prognosis of alcohol use in depressed patients (Foulds, Mulder et al. 2016).

2.3.2 Anxiety disorders

Anxiety disorders as a group are the most highly prevalent of psychiatric disorders (Somers, Goldner et al. 2006, Baxter, Scott et al. 2013). It has been estimated that 16.6% of people in developed nations suffer from at least one anxiety disorder during their lifetime and the reported past year prevalence rates have been even higher (Baxter, Scott et al. 2013, Somers, Goldner et al. 2006). There is very high rate of comorbidity of anxiety disorders in MDD patients (Brown, Campbell et al. 2001) and 57% of Finnish MDD patients suffer from anxiety disorder comorbidities (Melartin, Rytsala et al. 2002).

The etiological factors of depression with anxiety disorder comorbidity are not completely understood, but both conditions share risk-factors such as early life adversity arguably resulting in neuroendocrinological and neurophysiological changes (Cowan, Callaghan et al. 2016, Sild, Ruthazer et al. 2017) and similar patterns of emotion processing deficits (Kret, Ploeger 2015). There is some evidence that clinical anxiety disorder episodes may predict development of depression especially in females (Breslau, Schultz et al. 1995) and that clinical anxiety symptoms may decrease in increasing age in contrast to that with depressive symptoms (Almeida, Draper et al. 2012). Moreover, socioeconomic stressors (poor social support and financial strain) may be a risk factor especially for comorbid cases of depression and anxiety in contrast to each of the disorders alone (Almeida, Draper et al. 2012).

2.3.2.1 Anxiety disorders according to DSM-IV and DSM-5 diagnostics manuals

The DSM-IV anxiety disorder class includes the following anxiety disorders: generalized anxiety disorder (GAD), panic disorder (with or without agoraphobia), agoraphobia without history of panic disorder, specific phobias, social phobia (or social anxiety disorder), obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), acute stress disorder, anxiety disorder due to a general medical condition and anxiety disorder NOS (not otherwise specified). (American Psychiatric Association 1994)

Some changes were made for the DSM-5. The more pronounced changes were removing OCD and PTSD and including them in their own diagnostic classes and including separation anxiety and selective mutism in the anxiety disorder class. The DSM-5 diagnoses include: separation anxiety disorder, selective mutism, specific phobia, social anxiety disorder (social phobia), panic disorder (and panic attack specifier), agoraphobia, generalized anxiety disorder and substance/medication-induced anxiety disorder, anxiety disorder due to another medical condition, other specified anxiety disorder and unspecified anxiety disorder. (American Psychiatric Association 2013)

2.3.2.2 Panic disorder and agoraphobia

According to DSM-IV panic disorder is characterized by recurrent unexpected panic attacks with intense fear that include a number of somatic hyperarousal symptoms and as a disorder it is also described as including persistent concern about having additional attacks as a characteristic (American Psychiatric Association 1994). Agoraphobia is described as anxiety about being in places or situations from which escape might be difficult or in which help may not be available in the event of having an unexpected or situationally predisposed panic attack or panic-like symptoms (American Psychiatric Association 1994). These two disorders commonly coexist and approximately half of panic disorder patients also have agoraphobia (Wittchen, Reed et al. 1998). The past-year prevalence of panic disorder in Finnish general population is 1.9% and the prevalence in Finnish MDD patients 17%, the respective proportions for agoraphobia being 1.2% and 12% (Melartin, Rytsälä et al. 2002, Pirkola, Isometsä et al. 2005).

2.3.2.3 Social anxiety disorder

Social anxiety disorder (SAD) is characterized as representing excessive fear of social or performance situations in which embarrassment or negative judgements from others may occur (American Psychiatric Association 1994). Some researchers argue that there are two separate subtypes of SAD according to whether only performance situations are associated with anxiety or anxiety is caused by social interaction more generally (NaragonGainey, Prenoveau et al. 2016). The past-year prevalence of SAD in Finnish general population is estimated at 1.0% and the prevalence in Finnish MDD patients at 20% (Pirkola, Isometsä et al. 2005, Melartin, Rytsälä et al. 2002).

2.3.2.4 Generalized anxiety disorder

According to the diagnostics manual generalized anxiety disorder (GAD) is characterized by excessive, uncontrollable and often irrational worry, which interferes with daily living and is accompanied by a number of somatic symptoms (American Psychiatric Association 1994). According to the DSM-IV this diagnosis is excluded if the anxiety only presents during a depressive episode or if other more specific anxiety disorders would better explain the anxiety. However, in the DSM-5 the exclusion criterion concerning a concurrent depressive episode has been omitted (American Psychiatric Association 2013). The past-year prevalence of GAD in Finnish general population is 1.0% and the prevalence in Finnish MDD patients is 14% (Melartin, Rytsälä et al. 2002, Pirkola, Isometsä et al. 2005).

2.4 Course and outcome of MDD

MDD is a highly recurrent disorder and at least half of the patients that have MDE have at least one recurrent episode in their life-time (Burcusa, Iacono 2007). Often the course of MDD includes many recurrences and remissions of the symptoms (Burcusa, Iacono 2007, Kupfer 1991). Up to 50% of patients with depression do not respond to first antidepressant treatment and up to 20% may have a chronic course of depression with no remission of symptoms over a two-year period (Fava 2003). However, up to 32% of patients with depressive episode in primary-care samples may remit within six months even without treatment (Whiteford, Harris et al. 2013).

2.4.1 Sociodemographic and clinical factors

Although there are many known risk factors predisposing to depressive episodes as reported in 2.3.3.1, not all of them are associated with recurrence of depressive episodes and socio-economic factors may not be marked predictors of recurrence (Burcusa, Iacono 2007). The known risk factors predisposing to recurrent episodes of depression consist of the severity of the index episode, presence of psychiatric comorbidity and family history of psychopathology (Burcusa, Iacono 2007). Negative cognitions, high neuroticism, temperament, poor social support and stressful life events are also associated with higher recurrence of depression, but the causality between these associations has not been established (Burcusa, Iacono 2007, Farmer, Seeley 2009, Kampman, Poutanen 2011).

2.4.2 Complex depression

Complex or complicated depression refers to major depressive disorders that have higher treatment resistance, comorbidity with other disorders (e.g. somatic, anxiety, personality or substance use disorders) and high level of suicidality (Behn 2019, Clarkin, Petrini et al. 2019, Haverkamp, Arean et al. 2004, Rice, Halperin et al. 2017).

2.4.2.1 Alcohol use

Substance use disorder comorbidity in MDD patients is high and roughly one fourth of patients with MDD also have AUD (Davis, Uezato et al. 2008, Melartin, Rytsala et al. 2002). The associations explaining the comorbidity of MDD and SUDs are complex and the data available have suggested common predisposing factors and reciprocal causation between the two (Lyons, Schultz et al. 2006, Fergusson, Boden et al. 2011). It has been suggested that the most robust evidence shows that AUDs may causally predict depression (Fergusson, Boden et al. 2011, Boden, Fergusson 2011). Reflecting the reciprocal causation of MDD and AUD, in a prospective Finnish study the baseline severity of depression predicted AUDs at six months, which was further associated with less decline in depressive symptoms at 6 to 18-month follow-up (Melartin, Mantere et al. 2014). Alcohol use disorders may predispose to recurrences of depressive episodes and may interfere with the response to antidepressive treatment (Burcusa, Iacono 2007). The comorbidity of alcohol use disorder is also associated with chronic course of depression (Holzel, Harter et al.

2011). Emerging evidence suggests that simultaneous treatment of both disorders (MDD and AUD) is associated with better treatment outcomes (Agyapong 2013).

2.4.2.2 Personality and anxiety disorders as comorbidities

The comorbidity of anxiety disorders in depression is generally associated with poorer treatment outcome and higher recurrence of depressive episodes or more chronic course of the disease (Coplan, Aaronson et al. 2015, Burcusa, Iacono 2007, Sild, Ruthazer et al. 2017).

Although there are findings suggesting that the presence of personality disorder is associated with poorer outcome of antidepressive treatment and more chronic course of the disease, confirming these associations would need more studies with rigorous statistical methods (Bock, Bukh et al. 2010, Holzel, Harter et al. 2011, De Bolle, De Fruyt et al. 2011). Moreover, different personality disorders may have different effect on the outcome of depression and studying the associations between depression outcome and temperament and character dimensions could offer important new information on how individual personality is associated with the outcome of depression (Bock, Bukh et al. 2010, Holzel, Harter et al. 2011, De Bolle, De Fruyt et al. 2011).

2.4.3 Examples of treatment options for MDD with and without comorbidities

There are multiple general (national and international) guidelines for the treatment of MDD including comprehensive guidelines for the recognition and management of depression from the National Institute of Clinical Excellence (NICE, (Overview | Depression in adults: recognition and management | Guidance | NICE)) and the Canadian Network for Mood and Anxiety Treatments (CANMAT, (Kennedy, Lam et al. 2016)), a clinical practice guideline from the American College of Physicians (Qaseem, Barry et al. 2016), a two-part guideline for acute and maintenance treatment for depression from the World Federation of Societies of Biological Psychiatry (Bauer, Severus et al. 2015, Bauer, Pfennig et al. 2013), and the Finnish guideline concerning depression (Depression: Current Care Guidelines Abstract, 2016). The first-line treatment options for depression include pharmacotherapy with SSRIs and various psychotherapeutic interventions, which have been extensively studied and proven efficient in the treatment of MDD (Cuijpers, Sijbrandij et al.

2013). Second line treatment options for depression include SNRI, other agents affecting the monoamine system or ECT (McLoughlin, Kolshus et al. 2017, Vieta, Loft et al. 2017, Cipriani, Geddes et al. 2007, Gaynes, Warden et al. 2009). There is some evidence of positive effect on antidepressive treatment outcome by augmenting SSRI or SNRI medication with other pharmacological agents such as triiodothyronine (T3) (Nierenberg, Fava et al. 2006), lithium (Bschor 2014), omega-3-FAs (Mocking, Harmsen et al. 2016), antipsychotics (Zhou, Keitner et al. 2015) or by combining with a second antidepressant (Blier, Ward et al. 2010, Rush, Trivedi et al. 2011). The more novel treatment options with promising findings for depression include neuromodulatory treatments: repetitive transcranial magnetic stimulation (rTMS) (Zhao, Tor et al. 2018, Verma, Kumar et al. 2018), transcranial direct current stimulation (tDCS) (Palm, Hasan et al. 2016), vagus nerve stimulation (VNS) (Lv, Zhao et al. 2019), deep brain stimulation (DBS) (Dandekar, Fenoy et al. 2018), ketamine infusion therapy (Costi, Soleimani et al. 2019) and nasal esketamine (Daly, Trivedi et al. 2019).

The treatment options for depressed patients with anxiety disorder comorbidity are similar as for with patients without the comorbidity, but some more individualized treatment strategies according to the symptom profile have been proposed (Coplan, Aaronson et al. 2015). Both psychotherapy and pharmacotherapy are effective in the treatment of depressive and anxiety disorders either as monotherapy or used together (Cuijpers, Sijbrandij et al. 2013). However, there might be a minor preference of pharmacotherapy for dysthymia and of psychotherapy for obsessive-compulsive disorder in terms of efficacy (Cuijpers, Sijbrandij et al. 2013). One study suggests that anxiety comorbidity in depressed patients may be associated with better rTMS treatment outcome (Durmaz, Ebrinc et al. 2017). However, MDD patients' anxiety symptoms may not respond to ECT treatment even if the depression is alleviated (Huang, Lin et al. 2019).

In the next chapters, some common treatment methods of MDD are introduced in more detail. However, e.g. the details of different forms of psychotherapy, occupational therapy, neuromodulation techniques, or antidepressants apart from the most commonly used ones, are beyond the scope of this thesis.

2.4.3.1 Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine was the first SSRI developed in the 1970s and became more widely used in the treatment of MDD in the late 1980s and early 90s (Hillhouse, Porter 2015). Since then many other SSRIs have been developed including citalopram, sertraline,

paroxetine, escitalopram and fluvoxamine (Hillhouse, Porter 2015). Currently SSRIs are the most often prescribed antidepressants in European countries (Forns, Pottegård et al. 2019). The efficacy of all available SSRIs has been widely studied and a recent meta-analysis suggests a modest effect size for SSRIs in the treatment of MDD (Cipriani, Furukawa et al. 2018). However, fluoxetine is the only SSRI that has shown efficacy in the treatment of child and adolescent populations with MDD (Cipriani, Furukawa et al. 2018). The optimal fluoxetine equivalent dose in the treatment of MDD with SSRIs is suggested to be between 20-40mg (Furukawa, Cipriani et al. 2019).

Most SSRIs are efficacious in treatment of GAD, SAD, PTSD and OCD. However, the efficacy of SSRIs in the treatment of specific phobia is under studied and only small studies provide evidence for the efficacy of escitalopram and paroxetine. (Baldwin, Anderson et al. 2014)

SSRIs were primarily hypothesized to alleviate depression directly by inhibiting serotonin reuptake from the synaptic clefts and thus increasing the levels of serotonin in the CNS (Caldecott-Hazard, Morgan et al. 1991). However, this original theory has been proven inadequate to explain the antidepressant action of SSRIs and various secondary changes in the CNS have been suggested to cause the effects of SSRIs in alleviating depression (Caldecott-Hazard, Morgan et al. 1991). It has been proposed more recently that especially the use of SSRIs as antidepressants is associated with increase of BDNF in the limbic areas of the CNS (Dimitriadis, van den Brink et al. 2019). This effect could lead to neurotrophic consequences in the CNS (Maya Vetencourt, Sale et al. 2008) and would hypothetically result in alleviation of depression (Dimitriadis, van den Brink et al. 2019). There is evidence showing that serum BDNF concentrations increase after taking SSRIs (Zhou, Zhong et al. 2017) and that higher serum BDNF is associated with alleviation of depression in non-traumatized patients taking SSRIs (Dimitriadis, van den Brink et al. 2019). However, early life trauma could permanently reduce this hypothesized SSRI effect on BDNF (Dimitriadis, van den Brink et al. 2019).

2.4.3.2 Behavioral activation

Behavioral activation (BA) is a brief therapy that is effective in the treatment of MDD, also in comorbid or treatment resistant cases, or in patients with personality disorders (Bottonari, Roberts et al. 2008, Dimidjian, Hollon et al. 2006, Dobson, Hollon et al. 2008, Moradveisi, Huibers et al. 2013, Weinstock, Munroe et al. 2011). BA techniques include activity monitoring, assessment of goals and values and

activity scheduling, presenting a highly effective treatment for depression according to a meta-analysis (Cuijpers, van Straten et al. 2007).

2.4.3.3 Motivational interviewing

Motivational interviewing (MI) is a brief therapy that is effective as an adjuvant treatment in the treatment of various medical conditions and is most widely used in the management of substance use disorders (Fuangunyi 2019, DiClemente, Corno et al. 2017, Marker, Norton 2018). The hypothesized active elements of motivational interviewing include empathetic listening, non-judgemental attitude towards the patient, dialogue that is aimed to increase "change talk" and decrease "sustain talk" in patients, resulting in patients verbalizing reasons to change their habits (Miller, Rose 2009).

2.5 Dimensional approach to mood and anxiety disorders

Categorical methods for diagnosing psychiatric disorders has been the standard in the clinical and research settings thus far. The introduction of the DSM-III in the 1980s distinguished between anxiety disorders and depressive disorders and made diagnosing patients more explicit by introducing many new categories of disorders (American Psychiatric Association 1980). The development of such a categorical diagnostic manual has had a tremendous effect in aiding research on different psychiatric disorders and has helped the collaboration of clinical workers due to the relatively good reliability of the diagnoses (Surís, Holliday et al. 2016). The later diagnostics manuals have further developed the categorization of disorders according to the latest research data and one trend has been an increase in the number of recognized disorders. In the development process the criteria for some diagnoses have been changed and some diagnoses or subdivisions have also been removed – while new ones have been added (Surís, Holliday et al. 2016). In part due to the high number of different disorders, however, the validity of some diagnoses has been low (Surís, Holliday et al. 2016). In spite of the development of the diagnostics systems, the co-existence of more than one psychiatric disorder has been the new standard since the 1980s and it has been argued that more dimensional methods for describing psychopathology could better account for the challenges met in clinical situations (Surís, Holliday et al. 2016, Clark, Lee 2005).

In addition to categorical diagnosing of the patients, the dimensional assessment of patients' functionality or symptomatology in different disorders according to various scales has been common practice in clinical and research settings. The arguments supporting the use of these more linear methods of assessment have emphasized the importance of the effect that subthreshold symptomatology has on the patients' lives or prognoses and stressed that there would be a more linear association between the severity of different disorders and their outcomes (Karsten, Hartman et al. 2010, Zimmerman, Chelminski et al. 2012). These arguments have gained strength due to the lack of knowledge about or similarity of the etiological factors of different mood or anxiety disorders (Hughes, Heimberg et al. 2006, Watson, Clark et al. 1995, Clark, Lee 2005, Clark, Watson 1991). The categorical diagnoses may arguably advocate either too wide concepts of disorders, e.g., MDD, which is likely associated with a wide range of patients with different etiologies for the symptomatology and prognoses or too narrow concepts resulting in comorbidity of different disorders (e.g. MDD and generalized anxiety disorder) although the clinical syndrome could be better explained by a common etiology (Watson, David 2005, Ten Have, Lamers et al. 2016).

Comorbidity of mood and anxiety disorders has been especially high in clinical populations and in secondary level psychiatric clinics personality and substance use disorders also often co-occur with those affective disorders (Melartin, Rytsälä et al. 2002). This high comorbidity of different disorders has inspired researchers to develop more integrative and dimensional approaches to assess psychiatric disorders aimed to better concur with the likely etiologies of these disorders. Factor analyses of depressive and anxiety disorders have suggested two broader categories for these disorders (fear and anxiety-misery) and three dimensions of symptoms (Krueger 1999). More specifically the tripartite model suggested dimensions of general neurotic symptoms (common to depression and anxiety), somatic anxiety (specific to anxiety disorders) and low positive affect (specific to depression) (Clark, Watson 1991). Closely resembling two of the mentioned dimensions of symptoms (neurotic and positive affect), two higher order personality dimensions have been proposed to be important in association with psychopathology, namely neuroticism or negative affect and extraversion or positive affect (Clark, Lee 2005). These similarities have led some researchers to argue that personality or temperament dimensions could serve as a basis for an integrative model for psychopathology (Clark, Lee 2005).

2.6 Towards a dimensional approach to human personality and temperament

Although the categorical assessment of personality disorders has been the gold standard in clinical settings, over the past decades the scientific studies have utilized dimensional assessment of the personality for many decades. Perhaps because of the mounting evidence also supporting the clinical usefulness of the dimensionally assessed factors of personality the DSM-5 has included the possibility of dimensional assessment of personality disorders and the new version of the International Classification of Diseases (ICD-11) has replaced the former categorical diagnostics algorithm for personality disorders with a dimensional equivalent (Bach, Sellbom et al. 2018, WHO | International Classification of Diseases, 11th Revision (ICD-11), Bukh, Andersen et al. 2016, Joyce, McKenzie et al. 2007, Widiger, Mullins-Sweatt 2009).

2.6.1 Definition of concepts

The human temperament refers to individual predispositions for general mood and emotional responses that are based largely on genetically based biological processes and that are presented early in life (Rettew, McKee 2005, Rothbart, Ahadi 1994). Considering the early prelingual development of temperament, it is thought to represent a more biological pre-semantic core of the human personality (Cloninger, Svrakic et al. 1993). This biologically based temperamental core of personality is thought to remain fairly stable throughout an individual's life-span although some aspects of personality change/develop later in life in adaptation/maladaptation to changes in environment (Cloninger, Svrakic et al. 1993).

In a broad sense personality defines the consistent and unique way different individuals react and behave with respect to different situations in their lives. This definition of personality highlights two general aspects of how the modern psychological literature comprehends personality: 1) relatively consistent throughout the individual's life-span and 2) unique to different persons with individual presentations of traits distributed on dimensional continuums (Roberts, DelVecchio 2000). Personality is thought to be composed of various aspects of individual differences in needs, attitudes, motives, values, coping mechanisms, capabilities, attainments and self-esteem (Cervone, Pervin 2018). These cognitively more complex aspects of the human personality are thought to be moderated by

temperament and to develop over individual's life-span due to experiences in interaction with the environment (Cloninger, Svrakic et al. 1993).

According to trait theories of personality individuals are assumed to possess broader predispositions – called traits - to respond in different situations in unique ways. These traits are thought to be representative of the consistent differences in the patterns in which different individuals behave, feel or think in similar situations. According to these theories individuals' responses in specific situations represent habits when repeated in similar situations. Different habits are thought to form traits when combined with other similar habits and the groups of different traits are thought to form dimensions or factors when combined with other associated traits. (Cervone, Pervin 2018)

There are multiple different models of human personality with different numbers of personality trait dimensions based on statistical factor analyses of different personality traits. These models include the three-factor model and the five-factor model (FFM) of personality (Eysenck, Eysenck 1994, Costa, McCrae 1992). Due to the consistency of personality traits - also over time - personality profiles assessed with such instruments may be used to predict an individual's future reactions and behavior (Masse, Tremblay 1997).

2.7 The five-factor model of human personality

The new diagnostics algorithms of personality disorders in the DSM-5 and ICD-11 are based on the five-factor model (FFM) of personality although differences exist between the manuals (Bach, Sellbom et al. 2018). The algorithm in the DSM-5 includes dimensions of negative affectivity, detachment, antagonism, disinhibition and psychoticism, whereas the ICD-11 dimensions consist of negative affectivity, detachment, dissociality, disinhibition and anankastia (American Psychiatric Association 2013, WHO | International Classification of Diseases, 11th Revision (ICD-11). According to the five-factor model, however, the human personality consists of neuroticism, extraversion, openness, agreeableness and conscientiousness referred to as The Big Five trait factors (Costa, McCrae 1992). These factors are representative of the degree to which an individual has traits associated with: 1) emotional instability and negative emotionality (Neuroticism), 2) inclination to social interaction and positive emotionality (Extraversion), 3) proactive orientation and openness to new experiences (Openness), 4) being compassionate or antagonizing of others (Agreeableness), and 5) being persistent and organized

(Conscientiousness) (Costa, McCrae 1992). Costa and McRae introduced in 1992 the revised version of the NEO Personality Inventory (NEO-PI-R) for the assessment of 30 different traits that the model organizes into the five different personality domains (Costa, McCrae 1992). The five factors in the model have shown high internal consistency, interrater reliability and stability over time and the model has been used widely in various studies of general population as well as in clinical patient samples (Roberts, DelVecchio 2000). Although the factors of the five-factor model have shown substantial overlapping with some of the dimensions of Cloninger's biopsychological model of temperament and character, the two models also have dissimilarities (De Fruyt, Van De Wiele et al. 2000).

2.8 Cloninger's biopsychological model of temperament and character

Robert Cloninger's original unified biosocial model of personality proposed a model with three temperament dimensions, one of them being associated with behavioral inhibition (Harm Avoidance, HA), another with behavioral activation (Novelty Seeking, NS) and a third with maintenance of behavior (Reward Dependence, RD) (Cloninger 1986, Cloninger 1987). Whereas the personality dimensions of the FFM were based on lexical analysis of different personality traits, Cloninger's temperament dimensions were constituted based more on biological findings and animal studies (Cloninger 1986). In his theory Cloninger also stressed the importance of learning and social influences as being equally important as biological and genetic influences on personality development. In the proposal Cloninger described possible schemas by which the different temperament dimensions interact together to produce individual personality variants in interaction with life-events (Stallings, Hewitt et al. 1996). Temperament traits, per se, were assumed to be individually heritable and apparent early in life (Cloninger 1986). As originally proposed, the variation in each dimension would be related to monoaminergic activity (Cloninger 1986) i.e. NS with low basal dopaminergic activity, HA with high serotonergic activity and RD with low basal noradrenergic activity (Stallings, Hewitt et al. 1996).

For the assessment of the three temperament dimensions (HA, NS, RD) the Tridimensional Personality Questionnaire was introduced (TPQ; (Cloninger 1987)). However, studies with the TPQ indicated that the former RD subsection Persistence proved to be relatively independent of the original three temperament factors, and was therefore separated from RD to present a fourth temperament dimension called

Persistence (P) (Cloninger, Przybeck et al. 1994). To represent individual differences more adequately, the model was extended with three additional dimensions of the character, namely Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST) (Cloninger, Przybeck et al. 1994, Sigvardsson, Bohman et al. 1987, Gillespie, Cloninger et al. 2003, Cloninger, Svrakic et al. 1993). First the Temperament and Character Inventory (TCI) was introduced for the assessment of the seven personality dimensions and was followed by revised version (TCI-R) some years later (Cloninger, Svrakic et al. 1993, Pelissolo, Mallet et al. 2005). The revisions for the TCI-R included scoring of each item on a 5-point Likert scale, making changes to 51 items, adding three subscales to P and one to RD (Pelissolo, Mallet et al. 2005). TCI-R is thus a self-rated questionnaire that includes 240 items scored on a 5-point scale describing how well each item is representative of the subject (Pelissolo, Mallet et al. 2005).

The new enhanced biopsychological model of temperament and character made a distinction of temperament and character dimensions (Cloninger, Svrakic et al. 1993). Primarily Cloninger assumed that the character dimensions would be less inherited than temperament and that maturation of those traits would occur with age (Cloninger, Svrakic et al. 1993). However, the heritability of temperament and character dimensions has been almost equal and ageing seems to have an effect on both domains (Gillespie, Cloninger et al. 2003, Keller, Coventry et al. 2005, Calvet, Pericaud et al. 2016). A controversial 15-step model of personality development has been described (Cloninger, Svrakic 1997, Farmer, Goldberg 2008a).

2.8.1 Temperament and character dimensions

According to the biopsychological model of temperament and character, not even the extreme presentations of singular temperament traits inherently lead to better or worse adaptation and both extremes on each dimension also present adaptive qualities (Cloninger, Svrakic et al. 1993). The scores on each temperament dimension are normally divided in general population and the distribution of the scores represents the whole spectrum in the respective dimensions.

The Harm Avoidance (HA) dimension represents the temperamental bias the individual has with respect to the inhibition of behavior in response to signs of punishment. Individuals with high scores on the HA dimension are pessimistic, fearful, shy and fatigable while low scorers are optimistic, daring, outgoing and energetic (Cloninger 1987). HA is composed of subdimensions: Anticipatory Worry

(HA1), Fear of Uncertainty (HA2), Shyness (HA3), and Fatigability (HA4) (Pelissolo, Mallet et al. 2005).

The Novelty Seeking (NS) dimension represents the temperamental bias the individual has with respect to initiation or activation of appetitive behavior in response to novelty. Individuals with high scores on NS are exploratory, impulsive, extravagant and irritable, whereas low scorers present as reserved, deliberate, thrifty and stoical (Cloninger 1987). NS is composed of following subdimensions: Exploratory excitability (NS1), Impulsiveness (NS2), Extravagance (NS3), and Disorderliness (NS4) (Pelissolo, Mallet et al. 2005).

The Reward Dependence (RD) dimension represents the temperamental bias the individual has with respect to maintenance of behavior in response to cues of social reward. Individuals with high scores on RD are described as sentimental, open, warm and affectionate, while low scorers are described as detached, aloof, cold and independent (Cloninger 1987). RD is composed of subdimensions: Sentimentality (RD1), Openness to warm communication (RD2), Attachment (RD3), and Dependence (RD4) (Pelissolo, Mallet et al. 2005).

The Persistence (P) dimension represents the temperamental bias the individual has with respect to maintenance of behavior despite frustration. High scorers on P are industrious, determined, enthusiastic or perfectionist and low scorers lazy, spoiled or pragmatic (Cloninger, Svrakic et al. 1993). P is composed of subdimensions: Eagerness of effort (P1), Work hardened (P2), Ambitious (P3), and Perfectionist (P4) (Pelissolo, Mallet et al. 2005).

The character dimensions were included in the biopsychological model of temperament and character mainly in order to better assess the individual capacity for adaptation in society. Similarly the to temperament dimensions, the scores in the character dimensions are normally divided in the general population. However, low scores on character dimensions (especially in Self-Directedness (SD) and Cooperativeness (C)) are usually unfavorable to the individual whereas higher scores are associated with better adaptation. (Cloninger, Svrakic et al. 1993)

The Self-Directedness dimension represents the level of executive competence of an individual. Individuals with high scores on SD are self-sufficient, responsible, reliable, resourceful, goal oriented and self-accepting, whereas low scorers are blaming, helpless, irresponsible, unreliable, reactive and unable to set meaningful goals (Cloninger, Svrakic et al. 1993). SD is composed of subdimensions: Responsibility (SD1), Purposefulness (SD2), Resourcefulness (SD3), Self-acceptance (SD4), and Enlightened second nature (SD5) (Pelissolo, Mallet et al. 2005).

The Cooperativeness dimension represents the level of an individual's cooperation skills. Individuals with high scores on C are empathetic, tolerant, compassionate, supportive, and principled, while low scorers are self-absorbed, intolerant, critical, unhelpful, revengeful and opportunistic (Cloninger, Svrakic et al. 1993). C is composed of subdimensions: Social acceptance (C1), Empathy (C2), Helpfulness (C3), Compassion (C4), and Pure-hearted conscience (C5) (Pelissolo, Mallet et al. 2005).

The Self-Transcendence (ST) dimension represents the level of spiritual affiliation of an individual. Individuals with high scores on ST are described as judicious, insightful, spiritual, unpretentious and humble, and low scorers instead as pragmatic, objective, materialistic, controlling and pretentious (Cloninger, Svrakic et al. 1993). ST is composed of subdimensions: Self-forgetfulness (ST1), Transpersonal identification (ST2), and Spiritual acceptance (ST3) (Pelissolo, Mallet et al. 2005).

2.8.1.1 Heritability and genetics of temperament and character

Twin studies have provided estimates for the heritability of different domains of temperament and character. Although Cloninger primarily assumed that temperament would be more genetically predefined than character, studies addressing heritability have shown equal estimates for heritability for temperament dimensions 30%-57% and character dimensions 27-44% (Gillespie, Cloninger et al. 2003, Keller, Coventry et al. 2005). These estimates for heritability are similar to those found for other personality measurements e.g. Eysenck's Personality Questionnaire (Keller, Coventry et al. 2005). Although the genetic overlap between temperament and character is estimated at 11-30%, the majority of the genetic variance on each temperament and character dimension has been unique (Gillespie, Cloninger et al. 2003).

Although some studies have found an association between 5-HTTPLPR polymorphism and temperament dimension HA, meta-analyses of the available data have resulted in negative findings on the association (Munafò, Freimer et al. 2009, Minelli, Bonvicini et al. 2011). It has been suggested that including study subjects with mood and anxiety disorders would explain the association between 5-HTTPLPR and HA in studies with positive findings (Minelli, Bonvicini et al. 2011). Another genetic correlate with temperament on which meta-analytical data exists is that between DRD4 C-521T polymorphism and NS. According to a meta-analysis C-521T polymorphism accounts for 3% of the variance in NS, whereas Extroversion (according to the FFM) was not associated with the polymorphism (Munafò, Yalcin

et al. 2008). Although temperament and character are moderately heritable and some candidate gene studies have reported positive associations, genome-wide studies (GWAS) have resulted in null findings (Verweij, Zietsch et al. 2010, Munafò, Yalcin et al. 2008, Service, Verweij et al. 2012). It has been suggested that combining different personality trait items together to better refine personality phenotypes could aid in the genetic mapping of the personality (Service, Verweij et al. 2012).

2.8.1.2 Stability of temperament and character

The majority of the evidence on the stability of personality traits has come from studies with the Big Five personality domains (Roberts, DelVecchio 2000). In a meta-analysis of test-retest correlations of personality traits the trait consistencies were 0.31 in childhood, 0.54 during late adolescence/early adulthood, 0.64 at the age of 30 and 0.74 at ages 50-70, whereas the studied temperament dimensions showed lower consistency in the meta-analysis (Roberts, DelVecchio 2000). However, the studies on temperament included in the meta-analysis consisted mostly of studies on children and the existent evidence of the constancy of temperament in adulthood using Cloninger's temperament measures was completely missing (Roberts, DelVecchio 2000). The test-retest correlation for the TPQ temperament dimensions in adult population have ranged from 0.58 to 0.84 in a two-year follow-up (Heath, Bucholz et al. 1997). Adding to that data, there is some evidence of the constancy of temperament dimensions (TPQ) from childhood to adulthood, which has been suggested to indicate that the personality predispositions are stable adaptive tendencies, rather than fixed traits or gradually acquired habit patterns (Sigvardsson, Bohman et al. 1987).

In the first failed attempt to validate the English language version of the TCI-R in a population sample of Oregonian home-owners, severe criticism of the TCI-R and the seven-factor model of temperament and character was expressed because of the issues associated with the internal consistency of some of the dimensions (Farmer, Goldberg 2008b). However, overall the TCI-R has been adapted and validated in over twenty countries (e.g., (Pelissolo, Mallet et al. 2005) in France; (Martinotti, Mandelli et al. 2008b) in Italy; (Dzamonja-Ignjatovic, Svrakic et al. 2010) in Serbia; (Snopek, Hublova et al. 2012) in the Czech Republic; (Brändström, Richter et al. 2003) in Sweden and Germany; and (Giakoumaki, Karagiannopoulou et al. 2016) in Greece) with high coefficients of internal consistency (Fresán, Robles-García et al. 2011, Goncalves, Cloninger 2010, Tilov, Dimitrova et al. 2012, Brändström, Richter et al. 2003), test-retest reliability (Hansenne, Delhez et al. 2005,

Martinotti, Mandelli et al. 2008b, Pelissolo, Mallet et al. 2005), construct and predictive validity for personality disorders (Dzamonja-Ignjatovic, Svrakic et al. 2010, Fossati, Cloninger et al. 2007, Martinotti, Mandelli et al. 2008b). Subsequently also the English language version has been validated (Goncalves, Cloninger 2010). Although the earlier versions of the questionnaire (TPQ and TCI) have been validated in Finnish population, no systematic peer-reviewed evaluation of the revised version, TCI-R, in an adult Finnish population has been presented to date (Miettunen, Kantojärvi et al. 2004).

2.8.2 Temperament and character in depression

HA has repeatedly been higher in patients with MDD than in general population and HA correlates with depressive symptom scores in patients with MDD (de Winter, Wolterbeek et al. 2007, Farmer, Mahmood et al. 2003, Hansenne, Reggers et al. 1999, Hirano, Sato et al. 2002, Kimura, Sato et al. 2000, Marijnissen, Tuinier et al. 2002, Richter, Polak et al. 2003). High HA and more particularly its sub-scores anticipatory worry (HA1) and fatigability (HA4) have also manifested as trait-like markers for risk of depression i.e. either index episodes, relapses or recurrent episodes as well as impaired treatment response (Farmer, Seeley 2009, Kampman, Poutanen 2011, Balestri, Porcelli et al. 2019). So far, the findings concerning the associations of Reward Dependence in depressive symptomatology have been mixed (Farmer, Mahmood et al. 2003, Naito, Kijima et al. 2000, Peirson, Heuchert 2001, Farmer, Seeley 2009, Joffe, Bagby et al. 1993). However, low RD could be associated with treatment-resistant depression together with low P (Takahashi, Shirayama et al. 2013, Balestri, Porcelli et al. 2019), and together with high NS it is associated with dual diagnosis (i.e. concurrent mental illness and SUD) (Marquez-Arrico, Lopez-Vera et al. 2016). Combination of high HA and low SD is associated with suicide attempts in MDD patients, while these traits together with high NS and ST show similar association in depressed patients with bipolar disorder (Erić, Erić et al. 2017). In MDD patients with life-time alcohol dependency diagnosis NS seems to be higher and P and C lower than in MDD patients without alcohol dependency (Rae, Joyce et al. 2002). According to a recent meta-analysis high HA and low SD are found in patients with mood disorders (i.e. MDD and bipolar disorder), while patients with bipolar disorder have higher NS and ST than MDD patients (Zaninotto, Solmi et al. 2016).

MDD patients have lower SD and C scores than healthy controls and SD scores have a negative correlation with depressive symptom scores (Bensaeed, Ghanbari Jolfaei et al. 2014, Hur, Kim 2009, Nery, Hatch et al. 2009). In MDD patient's low SD is connected to childhood trauma, recurrence of depressive episodes and suicide attempts (Perna, Vanni et al. 2014, Asano, Baba et al. 2015, Erić, Erić et al. 2017). Further, low C could be associated with treatment resistance in depression (Balestri, Porcelli et al. 2019).

Decrease in HA and increase in C and SD during the first month and increase in SD and decrease in ST during first year of antidepressive treatment have been associated with better depression recovery in one earlier study (Corruble, Duret et al. 2002).

2.8.3 Temperament and character in substance use disorders

High NS is associated with substance use problems, predicts the development of SUD in high risk groups (Howard, Kivlahan et al. 1997, Sher, Bartholow et al. 2000), is related to alcohol use relapses in males and craving in substance dependence (Evren, Durkaya et al. 2012, Martinotti, Cloninger et al. 2008a, Zilberman, Tavares et al. 2003). Low NS instead may protect against the risk of familial alcoholism (Grucza, Cloninger et al. 2006). High HA has been connected to alcohol dependence (AD) and craving in substance dependent patients (Sher, Bartholow et al. 2000, De Los Cobos, Siñol et al. 2011), while dually diagnosed patients have higher NS than MDD patients (Fernandez-Mondragon, Adan 2015). More specifically, temperament profile with low RD and high NS together with low SD and C seems to be associated with dual diagnosis (Marquez-Arrico, Lopez-Vera et al. 2016).

SD seems to be lower in polysubstance users and low SD is associated with cluster B personality disorders (borderline-, antisocial-, histrionic-, and narcissistic personality disorders) in SUD patients (Yoon, Kim et al. 2007, Ball, Tennen et al. 1997). In another study with exclusively detoxified alcohol dependent (AD) male patients high scores on HA and ST, and low scores on P, SD and C predicted the severity of depression and anxiety (Evren, Evren et al. 2009).

2.8.4 Temperament in anxiety disorders

Two meta-analyses have addressed the associations of temperament and anxiety disorders and high Harm Avoidance has been associated with all anxiety disorders

with the notion of being especially high in Social phobia (SP, according to DSM-III) and Social anxiety disorder (SAD, according to DSM-IV) (Miettunen, Raevuori 2012, Kampman, Viikki et al. 2014).

Novelty Seeking has been at an intermediate level in Panic disorder (PD) or at low level in SP and SAD in patients with anxiety disorders (Kampman, Viikki et al. 2014, Miettunen, Raevuori 2012). Reward Dependence has shown a tendency to be at a higher level in patients with PD when compared to controls, but the results of studies are mixed, which could be explained by gender differences in the direction of the association (low RD for women and high RD for men) (Kampman, Viikki et al. 2014, Starcevic, Uhlenhuth et al. 1996).

In patients with SAD the results on RD have also been mixed and are on average at an intermediate level according to a meta-analysis (Kampman, Viikki et al. 2014). On Persistence patients with anxiety disorders have generally had intermediate scores, but Social phobia could be associated with low scores (Kampman, Viikki et al. 2014, Miettunen, Raevuori 2012). Generalized anxiety disorder is associated with high HA and impulsive symptoms in patients with GAD could be associated with high NS and low RD (Kampman, Viikki et al. 2014, Piero 2010).

2.8.5 Temperament and character as possible endophenotypes for MDD

Endophenotype is defined as a measurable entity of either neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological origin that is located between the genotype and the (clinical) phenotype in the association chain between the two (Gottesman, Gould 2003). Measurements with TCI-R could provide a neuropsychological endophenotype given that there are data supporting the association between both: 1) genetic markers, 2) psychiatric disorders and temperament and character dimensions (Munafò, Yalcin et al. 2008, Kampman, Poutanen 2011). However, although temperament and character have shown at least moderate heritability (Gillespie, Cloninger et al. 2003, Keller, Coventry et al. 2005), GWASs have been unable to recognize SNPs associated with temperament dimensions (Service, Verweij et al. 2012, Verweij, Zietsch et al. 2010). Similarly, GWASs have been unable to recognize replicable associations with affective disorders (Direk, Williams et al. 2017), and it has been suggested that more refined endophenotypes would be warranted to obtain significant genetic biomarkers for psychopathology in GWAS (Hamilton 2009, Service, Verweij et al. 2012).

2.9 Conclusions on the existing literature

It has been proposed that the symptoms of MDD consist of clusters with unique genetic background and that the individual clinical phenotype in depression is a combination of these different symptom clusters (Ginsburg, Werick et al. 1996). Earlier studies have provided data on the associations between 1) vegetative symptoms of depression (Okazaki, Tominaga et al. 2010, Kamata, Suzuki et al. 2011, Higuchi, Sato et al. 2008a, Higuchi, Sato et al. 2008b, Suzuki, Aoshima et al. 2005) or 2) temperament and character (Kampman, Poutanen 2011, Balestri, Porcelli et al. 2019) and depression outcome. Some studies have analyzed how combinations of different temperament dimensions are associated with depressive symptomatology (Matsudaira, Kitamura 2006, Grucza, Przybeck et al. 2003). However, the interactive effect of more complete temperament profiles and vegetative symptoms of depression on the short-term outcome of MDE has remained unstudied.

The data available on the differences in temperament and character dimensions between depressed patients and comorbid substance users is also limited (Rae, Joyce et al. 2002). Knowledge does exist on how temperament and character are associated with MDD and SUDs (Kampman, Poutanen 2011, Yoon, Kim et al. 2007) and one study has analyzed the association between changes in temperament and character dimensions and depression outcome (Corruble, Duret et al., 2002). However, no studies addressing the differences and possible changes over time in TCI-R dimensions in the acute phase of antidepressive treatment between depressed patients with or without comorbid substance abuse have been reported.

Although there is some data on how temperament and character are associated with depression outcome (Kampman, Poutanen 2011, Balestri, Porcelli et al. 2019, Farmer, Seeley 2009), the knowledge on how TCI-R dimensions' effect on the long-term outcome of depression is modulated by alcohol use comorbidity has remained unstudied to date.

Earlier studies and meta-analyses have provided data on how different temperament dimensions are associated with the risk of anxiety disorders (Kampman, Viikki et al. 2014, Miettunen, Raevuori 2012). It has been suggested that individual profile data with combinations of different dimensions of temperament could offer more comprehensive information on the associations between temperament and different anxiety disorders (Miettunen, Raevuori 2012). However, the associations between such more comprehensive temperament profiles and different anxiety disorders have not so far been studied.

3 AIMS OF THE STUDY

The general aim of this dissertation was to study temperament, character, and vegetative symptoms of depression as predictors of depression outcome and anxiety disorder comorbidity in depressed patients with or without alcohol use problems. More specific aims were set to study:

1. if temperament profile clusters together with vegetative symptoms of depression predict antidepressant treatment response at six weeks (Study I)

2. if severity of depression is associated with temperament profile clusters (Study I)

3. if there are differences in the temperament profiles of depressed patients with or without marked alcohol use problems (Study II)

4. which specific changes in temperament or character profiles predict treatment response during first six weeks of antidepressive treatment in depressed patients with or without marked alcohol use problems (Study II)

5. if temperament and character profiles (assessed after six weeks of antidepressive treatment) together with harmful alcohol use predict the outcome of depression over two-year follow-up (Study III)

6. if different temperament profile clusters are associated with the likelihood of Panic disorder and/or Agoraphobia, Social anxiety disorder or Generalized anxiety disorder in depressed patients (Study IV)

4 MATERIALS AND METHODS

4.1 Pharmacogenetic study on depression (the DEPGEN study) and Ostrobothnia Depression Study (the ODS study)

This thesis was conducted as a part of two larger studies. Study I is a part of the DEPGEN study and Studies II-IV are a part of the ODS study.

The DEPGEN study (Andre, Kampman et al. 2013) was conducted as an effort to study genetics and possible associated phenotypes in major depression. The study was funded mainly by Pirkanmaa and Kanta-Häme hospital districts and conducted in 2002-2006 in Pirkanmaa Hospital District catchment area (population 300,000).

The ODS study (Luoto, Lindholm et al. 2018, ClinicalTrials.gov Identifier NCT02520271) was conducted in South Ostrobothnia Hospital District (population 200,000) in Finland during the period 2009-2014. The aim of the ODS study was to evaluate the efficacy of a selected assessment and treatment protocol for depressed and dually diagnosed (depression and alcohol use disorder) patients and to study possible predictors of positive outcome of antidepressive treatment in this patient group.

4.2 Study design and subjects

Study I

Study I investigated a cohort of one hundred outpatients with major depressive episode recruited in Pirkanmaa Hospital District. Patients were evaluated and diagnosed by a psychiatrist and patients with current major depressive episode (MDE) according to DSM-IV criteria and MADRS scores of at least 20 (reflecting at least moderate depressive symptoms) were included in the study. The exclusion criteria consisted of severe somatic illness, psychosis, severe personality disorder, substance use disorders and medications likely to affect the patients' mood (antidepressive medications during past 3 months, or current use of mood stabilizing or antipsychotic medications). The patient cohort included adult patients aged 19-72

(mean±SD, 40.7±14.0) and 59 (59%) of the patients were female and the rest male. A more detailed description of the patient cohort is presented in Table 1.

The study protocol included three appointments in which sociodemographic data and baseline assessment of MADRS and TCI were collected at the first visit, adherence to treatment at the second visit (at 3-week timepoint) and endpoint data (MADRS scores) were collected at the third visit (at 6-week timepoint).

All patients were prescribed either citalopram, fluoxetine or paroxetine at baseline visit and the adherence to treatment was evaluated at the second visit. Patients were evaluated as adherent to treatment if they had used the prescribed medication on at least 80% of the days during the study period. The antidepressant dose was evaluated as fluoxetine equivalent daily doses in Studies I-IV. Eighty-six patients completed the study according to the protocol and were included in the main analysis of the depression outcome in Study I.

Table 1. Sociodemographic data of the DEPGEN patient sample

	Men		Women		Total	
	N	%	N	%	N	%
Total	41	41	59	59	100	100
Marital status[1]						
Single	14	34.1	21	35.6	35	35
Married or cohabiting	21	51.2	20	33.9	41	41
Divorced	6	14.6	14	23.7	20	20
Widowed	0	0	4	6.8	4	4
Education[2]						
Primary school	2	4.9	4	6.8	6	6
Comprehensive school	2	9.8	10	16.9	14	14
Tertiary education	9	22.0	10	16.9	19	19
Vocational school	16	39.0	9	15.3	25	25
Upper secondary education	7	17.1	19	32.2	26	26
Polytechnic or university	3	7.3	7	11.9	10	10
Work status before sick leave[3]						
Employed	24	58.5	31	52.5	55	55

Unemployed	7	17.1	10	16.9	17	17
Homemaker	0	0	5	8.5	5	5
Pensioner	5	12.2	5	8.5	10	10
Student	5	12.2	8	13.6	13	13

[1]χ^2=5.57, p=0.14; [2]χ^2=9.46, p=0.09; [3]χ^2=4.00, p=0.41; between genders

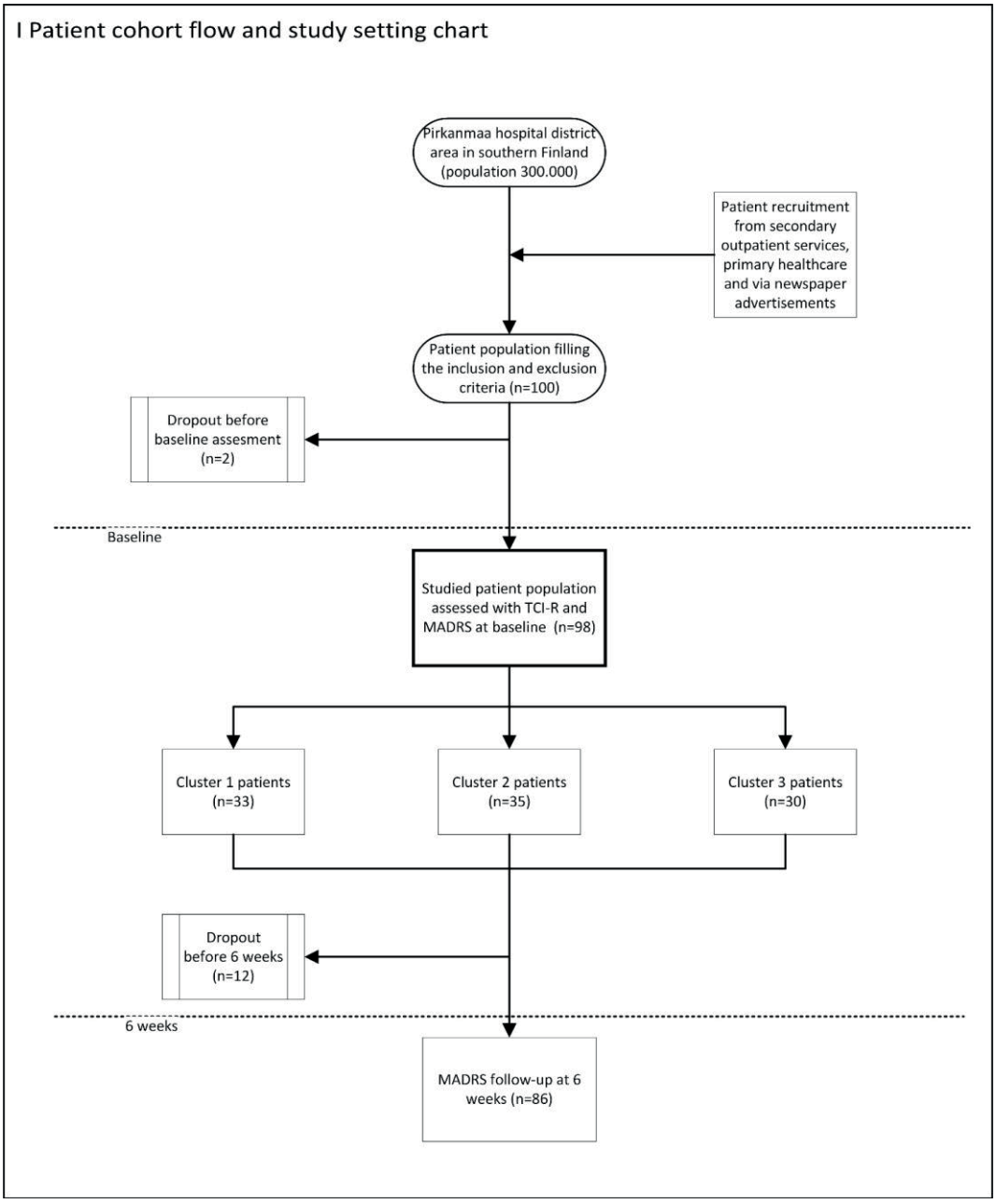

Figure 2 Patient cohort flow and study setting chart of Study I.

At baseline the patient cohort was divided into three patient clusters (i.e. Clusters 1,2 and 3) according to their temperament profiles (specific combinations of different temperament traits)

Abbreviations: TCI-R = Temperament and Character Inventory-Revised, MADRS = Montgomery-Åsberg Depression Rating Scale

Studies II-IV

The patient sample for Studies II-IV was recruited from patients referred to psychiatric specialized care due to depressive symptoms, anxiety, self-destructiveness, insomnia or alcohol-related problems. For inclusion in the study the patients had to have BDI scores of at least 17, reflecting at least moderate depressive symptoms. Exclusion criteria consisted of organic brain disease and likely or verified psychotic disorder. The recruited sample included 242 patients aged 17-64 years (38.6±12.2) and 148 (61.8%) of the patients were female and the rest male. At the screening patients completed the AUDIT questionnaire and were divided into two groups according to their scores: AUP (patients with marked Alcohol Use Problems, AUDIT ≥ 11) and non-AUP (AUDIT < 11). At the screening 99 (40.9%) of the patients met the criteria for AUP and the remaining 143 for non-AUP. The sociodemographic data of the patient cohort is presented in Table 2 and baseline BDI and AUDIT scores in Table 3.

Table 2. Sociodemographic data of the ODS patient sample

	Men		Women		AUP		non-AUP		Total	
	N	%	N	%	N	%	N	%	N	%
Total	94	38.8	148	61.2	99	40.9	143	59.1	242	100
Marital status[1]										
Single	34	36.2	39	29.1	38	41.8	35	25.9	73	32.3
Married or cohabiting	39	42.4	71	53.0	34	37.4	76	56.3	110	48.7
Divorced	19	20.7	21	15.7	19	20.9	21	15.6	40	17.7
Widowed	0	0	3	2.2	0	0	3	2.2	3	1.3
Education[2]										

Primary school	4	4.3	3	2.2	2	2.2	5	3.7	7	3.1
Comprehensive school	27	29.3	28	20.7	29	31.9	26	19.1	55	24.2
Tertiary education	10	10.9	25	18.5	11	12.1	24	17.6	35	15.4
Vocational school	33	35.9	54	40.0	36	39.6	51	37.5	87	38.3
Upper secondary education	10	10.9	7	5.2	5	5.5	12	8.8	17	7.5
Polytechnic or university	8	8.7	18	13.3	8	8.8	18	13.2	26	11.5
Work status before sick leave[3]										
Employed	39	42.9	67	50.0	39	43.3	67	49.6	106	47.1
Unemployed	41	45.1	30	22.4	38	42.2	33	24.4	71	31.6
Homemaker	0	0	10	7.5	0	0	10	7.4	10	4.4
Pensioner	5	5.5	11	8.2	4	4.4	12	8.9	16	7.1
Student	6	6.6	16	11.9	9	10.0	13	9.6	22	9.8
Self-reported history of depressive episode[4]	62	67.4	90	65.7	70	74.5	82	60.7	152	66.4

First degree family history of depression[5]	33	35.9	56	41.5	33	36.3	56	41.2	89	39.2
First degree family history of bipolar disorder[6]	4	4.3	10	7.4	5	5.5	9	6.6	14	6.2

Abbreviations: AUP = Alcohol Use Problems

[1]χ^2=11.12, p=0.011; [2]χ^2=6.95, p=0.23; [3]χ^2=14.04, p=0.007; [4]χ^2=4.68, p=0.031; [5]χ^2=0.55, p=0.457; [6]χ^2=0.12, p=0.73 between AUP and non-AUP, significant differences are in bold-face

Table 3. Baseline scores of BDI and AUDIT group-wise and in the complete cohort

	Men	Women	AUP	non-AUP	Total
Baseline BDI mean (±SD)	28.5 (6.80)	27.5 (7.59)	28.1 (6.95)	27.8 (7.55)	27.9 (7.30)
Baseline AUDIT mean (±SD)	15.1 (10.59)	7.9 (8.30)	20.8 (7.19)	3.7 (3.07)	10.7 (9.88)

Abbreviations: BDI = Beck Depression Inventory; AUDIT = Alcohol Use Disorder Identification Test; AUP = Alcohol Use Problems

The baseline assessments were conducted during appointments with a research nurse and a psychiatrist. At baseline data on patients' temperament profiles (TCI-R) and depressive symptoms (MADRS) were assessed and the patients were diagnosed using the Mini International Neuropsychiatric Interview 5.0 (MINI), validated diagnostic interview designed to be a short but accurate structured psychiatric interview (Sheehan, Lecrubier et al. 1998). In the follow-ups TCI-R and MADRS were assessed again at 6 weeks and MADRS also at 6 months and 24 months.

At baseline patients had an appointment with a psychiatrist where their medication was evaluated and changed if necessary. All patients received behavioral activation (BA) therapy and the AUP group also motivational interviewing (MI)

according to a specific treatment intervention procedure (see ClinicalTrials.gov Identifier NCT02520271). For a more detailed description of the patient sample see sections II and IV of this dissertation.

Dropout occurred before baseline assessments and before each of the follow-up timepoints. At baseline MADRS, MINI, and TCI-R were assessed in patients at two different appointments (with a research nurse and with a psychiatrist) and some data was missing on one or more of the measures. At baseline MADRS was assessed in 228 (94%), MINI in 219 (90%), and TCI-R in 216 (89%) patients. Some TCI-R data was also missing at the 6-week timepoint for similar reasons due to the naturalistic setting of the ODS study. After the dropout at the 6-week timepoint MADRS was assessed in 188 (78%) and TCI-R in 177 (73%) patients.

Studies II-IV were conducted according to an intention-to-treat protocol and all available data was used in the main analyses. The number of patients eligible for inclusion in the main analyses in Studies II-IV was determined for each study according to the relevant data available. The more detailed patient flow charts for Studies I-IV are presented in Figures 2-5.

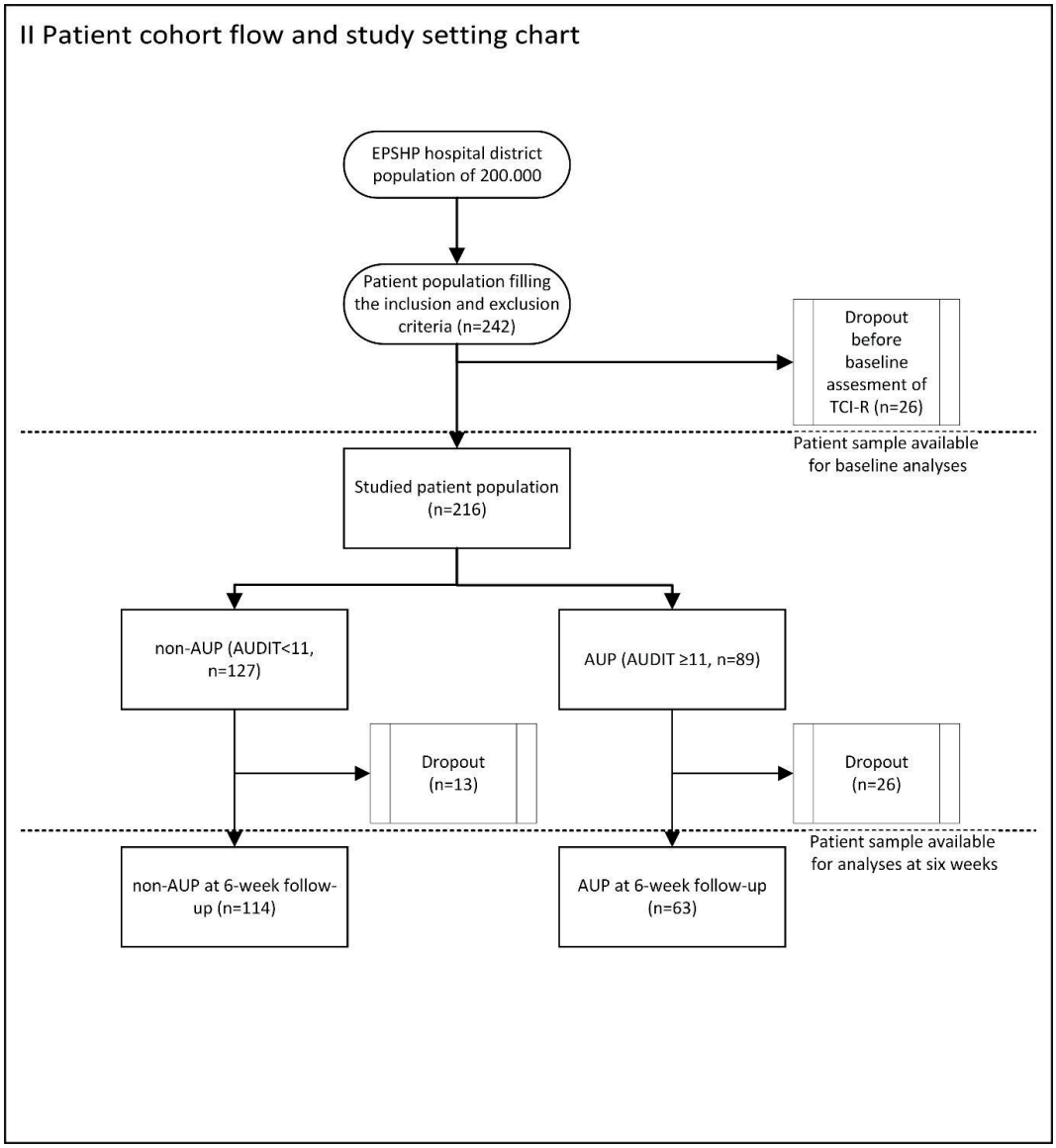

Figure 3 Patient cohort flow and study setting chart of Study II.

Abbreviations: AUP = Alcohol Use Problems, AUDIT = Alcohol Use Disorder Identification Test

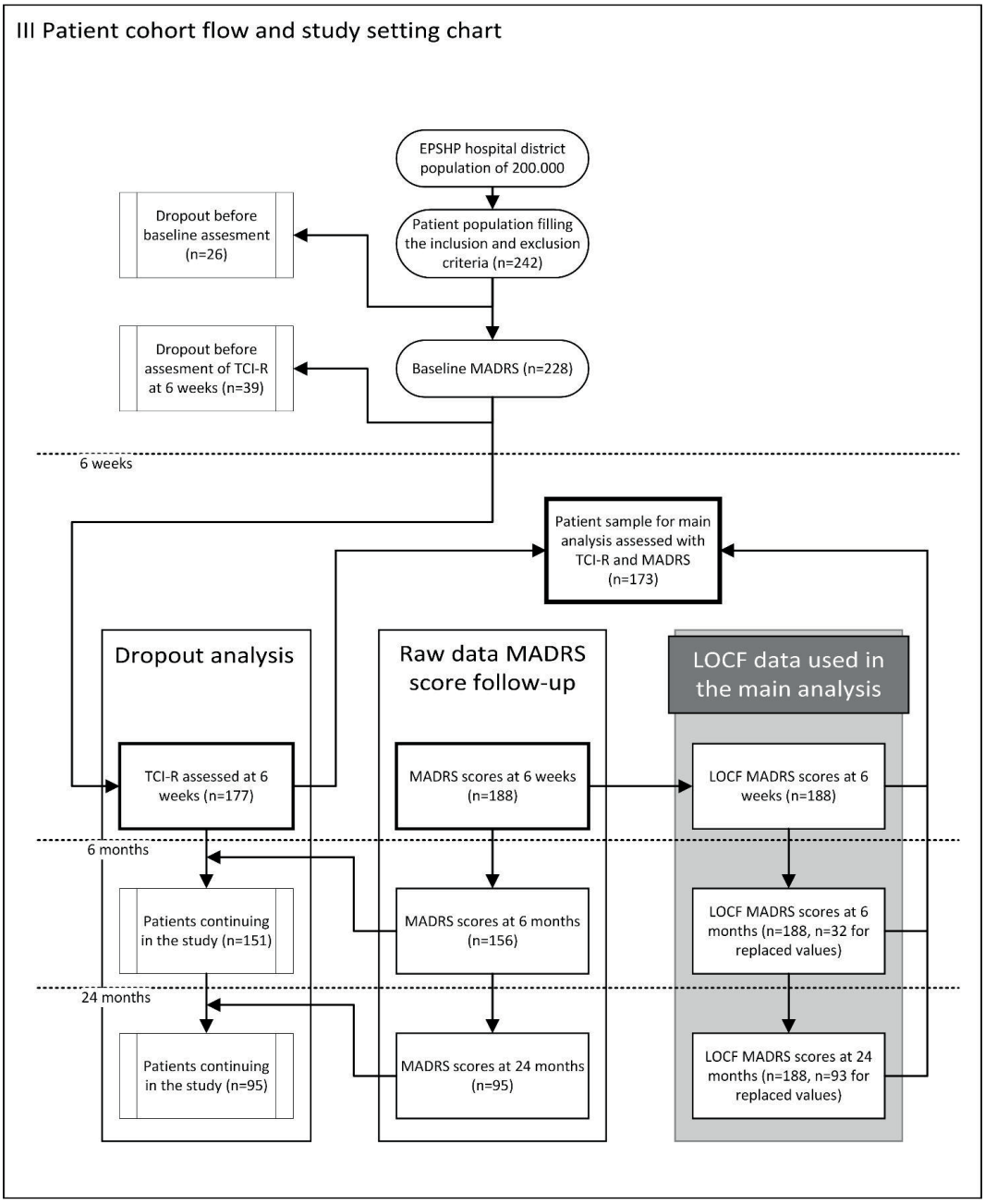

Figure 4 Patient cohort flow and study setting chart of Study III.

Abbreviations: TCI-R = Temperament and Character Inventory-Revised, MADRS = Montgomery-Åsberg Depression Rating Scale, LOCF = Last Observation Carried Forward

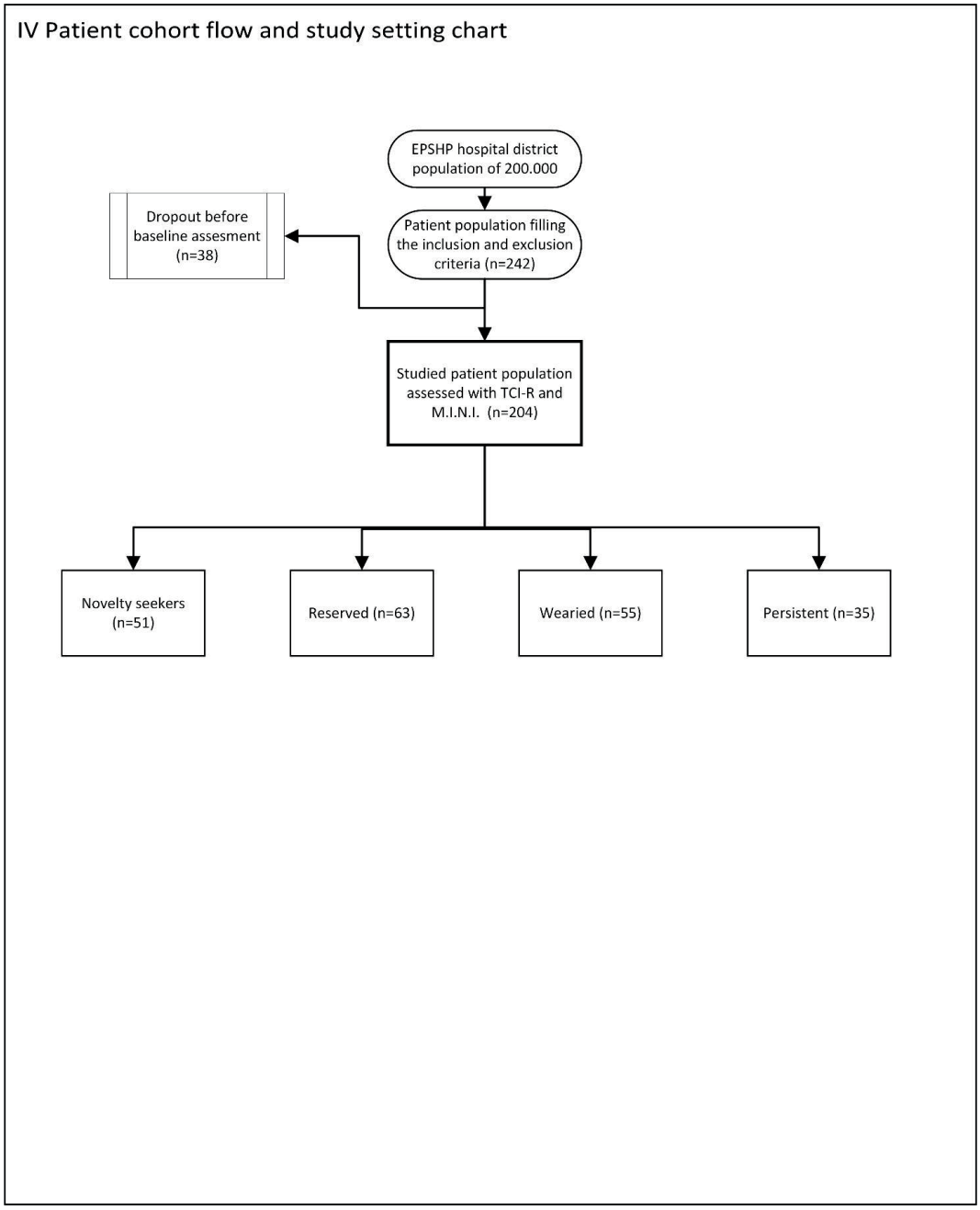

Figure 5 The patient cohort was divided into four patient clusters (i.e. Novelty seekers, Reserved, Wearied and Persistent) according to their temperament profiles in Study IV. See section 4.4 for the rationale to this approach.

Abbreviations: TCI-R = Temperament and Character Inventory-Revised, M.I.N.I. = MINI International Neuropsychiatric Interview

4.3 Measurements

The patients were screened for Studies II-IV with BDI (Beck et al. 1996) and AUDIT (Bohn et al. 1995) questionnaires. Other measurements included MADRS (Montgomery, Åsberg 1979) at different timepoints in all studies and the 107-item TCI temperament questionnaire (version IX) at baseline and at 6 weeks in Study I and the 240-item TCI-R at baseline and at 6 weeks in patients analyzed in Studies II-IV (Cloninger, Przybeck et al. 1994). In Study IV binary logistic regression models were built to predict the patients' comorbid anxiety disorders (MINI diagnoses). For the main analysis in Study I the vegetative symptoms of depression were assessed as the sum of questions 3-5 in the MADRS (see 2.2.2.1 and (Suzuki, Aoshima et al. 2005)). The other two factors are assessed as the sum of questions 1) 2, 9 and 10 for dysphoria and 2) 1, 6, 7, and 8 for retardation (Suzuki, Aoshima et al. 2005).

4.3.1 Outcome measures

Studies I-III were longitudinal follow-up studies predicting outcome of depression using MADRS scores or score changes at different timepoints and in Study III linearly from 6 weeks to 6 months and to 24 months as outcome measures.

The outcome measure in the main analysis of Study I was MADRS score at 6-week follow-up timepoint. (I)

Study II had two sets of main analyses. In the first part of the study the main outcome measures were TCI-R dimension scores at baseline and at 6 weeks. The second set of main analyses predicted the change in the symptoms of depression from baseline to the 6-week follow-up (ΔMADRS). (II)

Due to marked dropout in the follow-up, especially before the 24-month follow-up timepoint, the last observation carried forward (LOCF) method for data completion was performed for the main analysis in Study III. The primary outcome measures in the study were LOCF MADRS total score at 6 weeks, 6 months, and 24 months. (III)

Study IV included a cross-sectional analysis predicting comorbid panic disorder and/or agoraphobia, social anxiety disorder, and generalized anxiety disorder MINI diagnoses. (IV)

4.4 Statistical analyses

Cronbach's α was calculated to assess the reliability of each TCI-R dimension in the ODS patient cohort. In Studies I and IV a two-step cluster analysis was used to determine patients' temperament profiles. In the first step this method identifies groupings with a quick cluster algorithm and in the second step it runs a hierarchical cluster model. In Study I cluster analyses of all four temperament dimension scores (HA, RD, NS, and P) and of three temperament dimension scores (HA, RD, and NS) were both explored. Cluster analysis of the three temperament dimensions with number of clusters set as three showed highest quality for the clusters (i.e. higher number of temperament dimensions surpassing critical values in cluster analysis) and was therefore used in the main analysis of the study. In Study IV scores on each temperament dimension (NS, HA, RD, and P) were used in the clustering model and number of clusters was set to automatic to ensure natural clustering.

In all studies the differences between discreet variables (MADRS total score (I-IV), MADRS factor scores (i.e. vegetative, dysphoric and retardation) (I), antidepressant dose (as fluoxetine equivalent) (IV), AUDIT-C score and age (I-IV)), and grouping variables (temperament clusters (I and IV)) were calculated with ANOVA. Differences between grouping variables in each study were calculated with χ^2-statistics. (I-IV) In each study Pearson's correlation coefficients were calculated between MADRS total scores (and vegetative symptom scores (I)) and other clinical variables to explore potential covariates for general linear models (GLMs). These multiple analyses could arguably have posited a need for correction used for multiple testing. However, the main analyses were performed with GLMs and no correction was used.

The main analysis with linear mixed effects model in Study III was performed with PROC MIXED, SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and all other analyses (in Studies I-IV) were performed with current versions of SPSS for Windows or SPSS for Mac software (versions 17.0-24.0, IBM Inc., Armonk, New York, USA).

Study I

In Study I non-parametric tests were performed in comparisons of ordinal variables (patient compliance and medication prescribed) between the temperament clusters. Multi-nominal logistic regression model was used to analyze the possible effect of gender, severity of depression, prescribed antidepressant and dose, adherence to

treatment (use of medication on at least 80% of the days), and earlier depressive episode on the clusters. Two linear regression models (ANCOVA) with 1) temperament clusters and age, and 2) temperament clusters, age and baseline MADRS vegetative symptom scores were used to predict endpoint (at 6-week timepoint) MADRS total scores.

Study II

Independent samples t-tests were performed to analyze differences in TCI-R, MADRS, and AUDIT scores between AUP and non-AUP, between genders and in the dropout analysis. The changes in MADRS and TCI-R dimension scores between baseline and 6-week measurements were analyzed with paired samples t-tests.

GLMs were used in the main analyses to better address the potential collinearity of the predictors (Dormann, Elith et al. 2013). In the first type of GLM analyses in Study II age, gender, and AUP were used as explanatory variables in predicting each of the TCI-R dimension scores (NS, HA, RD, P, SD, C, ST) at baseline and at 6 weeks.

The second type of GLM analyses predicted MADRS score change from baseline to 6 weeks (ΔMADRS) with age, gender, and AUP together with either 1) temperament dimension changes (ΔNS, ΔHA, ΔRD, ΔP) or 2) character dimension changes (ΔSD, ΔC, ΔST) used as explanatory variables.

Study III

In the dropout analysis differences in discreet variables between dropouts and other patients were calculated with independent samples t-tests. Data imputation for the main analysis was made with the LOCF method, which replaced missing values in MADRS scores in 32 (17%) cases at 6-month and in 93 (49%) cases at 24-month follow-up timepoints. According to this method missing values are replaced with their last observed values in earlier follow-up timepoints.

A linear mixed effects model was used in the main analysis of the study. In this model the scores of the seven temperament and character dimensions (NS, HA, RD, P, SD, C, and ST; at six weeks) were used as explanatory variables to predict LOCF MADRS scores from 6 weeks to 6 months and to 24 months. The model was adjusted for AUP, gender, and AUP x gender and AUP x time interactions and individual-specific intercept and slope terms were used in the model. The -2 log likelihood information criteria were used to evaluate model fit and model with

unstructured covariance structure was reported. Kenward-Roger adjustment of degrees of freedom was applied for estimates of fixed effects.

Study IV

To analyze the effects of possible confounding variables on the dependent diagnosis three tiers of binary logistic regression models were used. Model 1 was adjusted for age and gender, Model 2 was adjusted for age, gender, and MADRS scores, and Model 3 was adjusted for age, gender, MADRS scores, and AUDIT-C scores. Panic disorder and/or agoraphobia (PDA), social anxiety disorder (SAD) or generalized anxiety disorder (GAD) were predicted in Models 1-3 with a temperament cluster that had the highest prevalence of the dependent diagnosis (see Table 8.) set as the explanatory variable.

4.5 Informed consent and ethical approvals

Informed consent was obtained from all participants included in this study. Approval for the study protocol was obtained from local ethics committees from Pirkanmaa (for DEPGEN) and from South Ostrobothnia (for ODS). Trial registration considering ODS was done through the Clinicaltrials.gov with identifier number NCT02520271.

5 RESULTS

5.1 Temperament clusters and vegetative symptoms of depression as predictors of antidepressant response (I)

The two-step cluster analysis of the DEPGEN cohort resulted in three clusters of patients with different temperament profiles. The first cluster (n=33) had a temperament profile with low NS, high HA and low RD (LNS/HHA/LRD), the second cluster (n=35) had intermediate NS, high HA, and high RD (INS/HHA/HRD), and the third cluster (n=30) had high NS, low HA, and high RD (HNS/LHA/(HRD)). RD did not reach statistical significance in one of the clusters and is therefore here presented in parentheses. Two of the clusters had temperament profiles with HA scores higher than NS scores in contrast to the third cluster, which had NS scores higher than HA scores and the first cluster showed the strongest sloping in the temperament dimension scores. The temperament dimension scores of the three clusters are reported in Figure 6 and the total MADRS score and sub-scores of the temperament clusters are presented in Table 4.

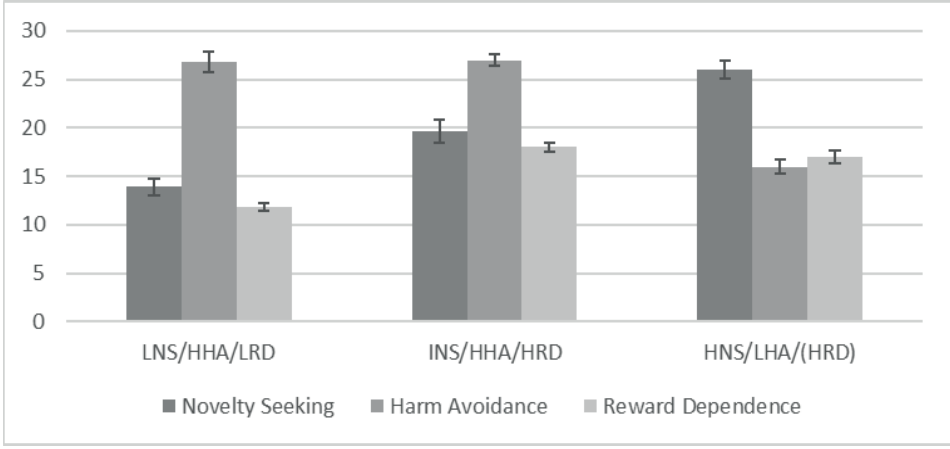

Figure 6 Temperament dimension (Mean±S.E.) scores of the three temperament clusters in DEPGEN cohort.

Abbreviations: LNS = Low Novelty Seeking, HHA = High Harm Avoidance, LRD = Low Reward Dependence, INS = Intermediate Novelty Seeking, HRD = High Reward Dependence, HNS = High Novelty Seeking, LHA = Low Harm Avoidance

We built two linear regression models to predict the endpoint MADRS scores. In the first model age and temperament clusters were used as explanatory variables. The whole model predicted 10% of variance in the endpoint MADRS scores ($p=0.04$; power 0.69) and the temperament clusters predicted individually 9% of the variance in endpoint MADRS ($p=0.02$), whereas age was a non-significant predictor of the outcome ($p=0.36$). In the second model the vegetative symptoms of depression at baseline were used as explanatory variable among temperament clusters and age. This model predicted 20% of the variance in the endpoint MADRS scores ($p=0.001$; power 0.96) and in this model vegetative symptoms of depression at baseline predicted 12% ($p=0.001$), temperament clusters 5% ($p=0.12$), and age 0.2% ($p=0.70$) of the variance.

A high correlation was observed between total MADRS score and the vegetative symptom scores both at baseline ($r=0.73$, $p<0.001$) as well as at endpoint ($r=0.76$, $p<0.001$). The correlations between baseline vegetative symptom scores and endpoint total scores in MADRS were moderate ($r=0.38$, $p<0.001$) and the association between baseline vegetative scores and the change in the total scores of MADRS from baseline to endpoint non-significant ($r=0.13$, $p=0.26$).

Table 4. Total and sub-factor MADRS scores for each temperament cluster at baseline and at 6 weeks

Cluster	LNS/HHA/LRD	INS/HHA/HRD	HNS/LHA/(HRD)
Baseline MADRS score (mean±SD)*	28.3 ± 6.1	27.3 ± 5.7	25.0 ± 4.4
Factor 1 (dysphoria)	8.5 ± 2.6	7.8 ± 2.2	7.4 ± 1.4
Factor 2 (retardation)	11.7 ± 2.2	12.1 ± 2.7	11.0 ± 2.9
Factor 3 (vegetative symptoms)	7.8 ± 3.1	7.4 ± 2.8	6.4 ± 2.7
MADRS scores at 6 weeks (endpoint)**	14.1 ± 9.1	13.5 ± 8.3	8.3 ± 5.5
Factor 1 (dysphoria)	3.7 ± 3.2	3.9 ± 2.7	2.5 ± 1.9
Factor 2 (retardation)**	6.3 ± 4.5	6.0 ± 3.7	3.4 ± 3.0
Factor 3 (vegetative symptoms)	3.5 ± 2.3	3.7 ± 2.9	2.4 ± 1.9

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; L = low; H = high; I = intermediate

*p=0.05 between groups (ANOVA)

**p=0.01 between groups (ANOVA)

The patients in the first cluster were older than those in the two other clusters, but there were no differences in other clinical variables tested (dosages of medications taken in weeks 1-3, p=0.48, compliance with treatment between the clusters, p=0.69). The mean ages for the patients in each cluster were: cluster 1 = 45.9±11.4, cluster 2 = 37.4±14.4, cluster 3 = 38.2±15.3; mean±SD, p=0.03 for the difference in ANOVA. Age showed a trendlike effect (p=0.051) on the clusters in the multinominal regression model, whereas gender, severity of depression, adherence to antidepressant treatment or antidepressant dose, adherence to treatment, and earlier depressive episode were non-significant predictors.

5.2 Effect of alcohol use problems on temperament and character profiles and antidepressive treatment response (II)

Internal consistencies were estimated as Cronbach's alphas for each baseline TCI-R dimension in the ODS patient cohort: NS 0.85, HA 0.88, RD 0.89, P 0.92, SD 0.86, C 0.85, ST 0.85. The differences in temperament and character profiles between patients with or without marked alcohol use problems (AUP and non-AUP) are presented in Tables 5 and 6. These tables present both the baseline and endpoint scores of each TCI-R dimension and the MADRS scores and changes therein also group-wise and for each of the genders separately. The patients in the AUP group had higher Novelty Seeking (p=0.001, ANOVA), lower Persistence (p=0.021), lower Self-Directedness, and lower Cooperativeness (p=0.001) than the non-AUP group at baseline. The differences were significant for NS (p=0.014, ANOVA) and SD (p<0.001) between the groups at six weeks.

Table 5. Comparison of temperament dimension scores between groups at baseline and 6 weeks and changes therein

		NS (±SD)	HA (±SD)	RD (±SD)	P (±SD)
All patients	Baseline (n=216)	100.19 (17.02)	114.82 (19.18)	99.45 (16.97)	100.59 (20.49)
	6 weeks (n=177)	99.72 (16.70)	113.43 (18.90)	100.05 (17.58)	99.72 (21.52)
	Change; p*	ns	ns	ns	ns
Men	Baseline (n=88)	104.35 (17.57)[1]	115.15 (18.26)	93.80 (16.39)[2]	98.58 (20.65)
	6 weeks (n=70)	103.31 (17.92)[3]	111.46 (16.90)	94.74 (17.15)[4]	99.33 (20.76)
	Change; p*	ns	-3.46; 0.010	ns	ns
Women	Baseline (n=128)	97.34 (16.09)[1]	114.59 (19.85)	103.34 (16.31)[2]	101.97 (20.35)
	6 weeks (n=107)	97.36 (15.50)[3]	114.72 (20.07)	103.52 (17.06)[4]	99.98 (22.09)
	Change; p*	ns	ns	ns	-2.15; 0.049
non-AUP	Baseline (n=127)	97.05 (17.41)[5]	113.71 (19.49)	100.69 (17.31)	103.28 (20.78)[6]

	6 weeks (n=114)	97.44 (16.95)[7]	112.44 (19.27)	100.97 (17.30)	102.02 (21.84)
	Change; p*	ns	ns	ns	ns
AUP	Baseline (n=89)	104.69 (15.47)[5]	116.40 (18.72)	97.67 (16.40)	96.74 (19.54)[6]
	6 weeks (n=63)	103.84 (15.53)[7]	115.22 (18.22)	98.38 (18.11)	95.57 (20.44)
	Change; p*	ns	ns	ns	ns

Abbreviations: AUP = Alcohol use problems; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; P = Persistence; ns = non-significant

Mean differences at baseline between men and women (±SD): [1]-7.02 (2.31), p=0.003; [2]9.54 (2.26), p<0.001

Mean differences at baseline between non-AUP and AUP (±SD): [5]-7.64 (2.30), p=0.001; [6]6.54 (2.80), p=0.021

Mean differences at 6 weeks between men and women (±SD): [3]-5.95 (2.54), p=0.020; [4]8.78 (2.63), p=0.001

Mean differences at 6 weeks between non-AUP and AUP (±SD): [7]-6.40 (2.59), p=0.014

*Change from baseline to 6 weeks with paired samples t-test

Table 6. Comparison of character dimensions and MADRS scores between groups at baseline and 6 weeks and changes therein.

		SD (±SD)	C (±SD)	ST (±SD)	MADRS (±SD, n)
All patients	Baseline (n=216)	122.30 (18.42)	131.17 (18.85)	66.63 (13.97)	23.13 (6.35, n=213)
	6 weeks (n=177)	125.36 (17.29)	131.89 (18.04)	64.93 (15.54)	17.05 (8.01, n=179)
	Change; p*	2.29; 0.015	ns	-1.71; 0.014	-6.38; <0.001
Men	Baseline (n=88)	117.86 (17.04)[1]	123.97 (19.26)[2]	65.91 (13.64)	24.72 (6.22, n=88)[3]
	6 weeks (n=70)	120.54 (16.35)[4]	125.10 (18.17)[5]	66.03 (14.44)	18.76 (7.81, n=74)[6]
	Change; p*	ns	ns	ns	-6.51; <0.001
Women	Baseline (n=128)	125.35 (18.78)[1]	136.12 (16.94)[2]	67.12 (14.21)	22.01 (6.22, n=125)[3]
	6 weeks (n=107)	128.50 (17.23)[4]	136.33 (16.59)[5]	64.21 (16.25)	15.85 (7.97, n=105)[6]
	Change; p*	2.30; 0.047	ns	-2.71; 0.004	-6.28; <0.001
non-AUP	Baseline (n=127)	125.63 (18.94)[7]	134.63 (17.91)[8]	67.47 (14.67)	22.68 (6.21, n=126)

	6 weeks (n=114)	129.27 (16.14)[9]	133.64 (17.57)	65.71 (16.13)	17.00 (7.98, n=115)
	Change; p*	3.54; 0.002	ns	-2.39; 0.005	-5.90; <0.001
AUP	Baseline (n=89)	117.55 (16.63)[7]	126.22 (19.16)[8]	65.42 (12.88)	23.77 (6.53, n=87)
	6 weeks (n=63)	118.27 (17.16)[9]	128.71 (18.57)	63.52 (14.43)	17.14 (8.13, n=64)
	Change; p*	ns	ns	ns	-7.22; <0.001

Abbreviations: AUP = Alcohol use problems; SD = Self-Directedness; C = Cooperativeness; ST = Self-Transcendence; ns = non-significant; MADRS = Montgomery-Åsberg Depression Rating Scale

Mean differences at baseline between men and women (±SD): [1]7.49 (2.51), p=0.003; [2]12.15 (2.48), p<0.001; [3]-2.71 (0.87), p=0.002

Mean differences at baseline between non-AUP and AUP (±SD [7]8.08 (2.49), p=0.001; [8]8.41 (2.55), p=0.001

Mean differences at 6 weeks between men and women (±SD): [4]7.96 (2.60), p=0.003; [5]11.23 (2.65), p<0.001; [6]-2.91 (1.20), p=0.016

Mean differences at 6 weeks between non-AUP and AUP (±SD): [9]11.00 (2.59), p<0.001

*Change from baseline to 6 weeks with paired samples t-test

The first type of GLMs used the possible predictors of temperament and character dimension scores (age, gender, AUP, and baseline scores of MADRS) as explanatory variables. These models had each of the TCI-R dimensions separately at baseline or at 6 weeks as the target variable. In these models AUP was a significant predictor of NS (p=0.027) and SD (p=0.016) at baseline and of P (p=0.047) and SD (p=0.001) at six weeks. All predictors and their explanatory proportions of these GLMs are presented in Table 7.

Table 7 is printed on the following two pages.

Table 7. GLM results with explanatory proportions for each individual explanatory variable (age, gender, AUP, and MADRS baseline scores) illustrating their contribution to temperament and character dimension scores at baseline and at 6 weeks

		NS baseline	NS 6 weeks	HA baseline	HA 6 weeks	RD baseline	RD 6 weeks	P baseline	P 6 weeks	SD baseline	SD 6 weeks	C baseline	C 6 weeks	ST baseline	ST 6 weeks
Age	ηp^{2**}	**0.097**	**0.082**	0.004	<0.001	0.011	0.009	**0.025**	0.006	**0.103**	**0.083**	**0.062**	**0.059**	0.017	**0.031**
	p	**<0.001**	**<0.001**	0.355	0.960	0.122	0.214	**0.022**	0.319	**<0.001**	**<0.001**	**<0.001**	**0.001**	0.061	**0.020**
gender	ηp^{2**}	**0.026**	0.015	0.001	**0.024**	**0.051**	**0.033**	0.001	0.003	0.014	0.008	**0.061**	**0.066**	0.002	0.001
	p	**0.018**	0.105	0.605	**0.043**	**0.001**	**0.018**	0.590	0.442	0.083	0.249	**<0.001**	**0.001**	0.541	0.621
AUP	ηp^{2**}	**0.023**	0.017	0.006	0.015	0.001	0.002	0.017	**0.023**	**0.028**	**0.066**	0.011	<0.001	0.002	0.008
	p	**0.027**	0.089	0.270	0.113	0.647	0.570	0.057	**0.047**	**0.016**	**0.001**	0.129	0.987	0.483	0.235
MADRS	ηp^{2**}	0.001	<0.001	0.021	0.018	**0.057**	**0.053**	<0.001	0.003	**0.036**	**0.028**	**0.024**	0.021	0.002	0.020
baseline scores	p	0.726	0.869	0.036	0.078	**<0.001**	**0.002**	0.852	0.487	**0.006**	**0.028**	**0.026**	0.057	0.479	0.062
Complete	ηp^{2*}	**0.157**	**0.124**	0.029	0.040	**0.132**	**0.111**	**0.050**	0.031	**0.180**	**0.200**	**0.176**	**0.157**	0.026	**0.063**
model	p	**<0.001**	**<0.001**	0.185	0.136	**<0.001**	**<0.001**	**0.031**	0.244	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.248	**0.025**
	power	**1.000**	**0.984**	0.479	0.533	**0.998**	**0.970**	**0.746**	0.423	**1.000**	**1.000**	**1.000**	**0.998**	0.421	**0.770**

Abbreviations: AUP = Alcohol Use Problems; MADRS = Montgomery Åsberg Depression Rating Scale; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; P = Persistence; SD = Self-Directedness; C = Cooperativeness; ST = Self-Transcendence

* ηp^2= explanatory proportion of the complete model for the target variable; ** ηp^2= explanatory proportion of the single factor or covariate for the target variable; AUP = alcohol use problems; MADRS = Montgomery-Åsberg Depression Rating Scale

Statistically significant results are presented in bold face

The second type of GLMs predicted change in the MADRS scores from baseline to 6 weeks (ΔMADRS) with either temperament or character dimension delta scores together with age, gender, and AUP set as explanatory variables. The temperament model predicted 12.2% (p=0.003) of the variance in ΔMADRS and in the model ΔRD 14.1% (p=0.005) and age 11.6% (p=0.012) were the only individual predictors of the outcome. The character model predicted 13.7% (p=0.001) of the variance in ΔMADRS and in the model ΔSD and ΔST were the only individual predictors of the outcome. Both models, without the AUP set as an explanatory variable, were then applied to AUP and non-AUP patients separately. The temperament model was non-significant in predicting ΔMADRS in non-AUP (p=0.141), but highly significant when the model was applied to AUP patients and predicted 28.3% (p=0.006) of the variance of ΔMADRS in this patient group. The character model predicted 14.3% (p=0.007) of ΔMADRS in non-AUP and in the model ΔSD (8.0%, p=0.003) and ΔST (5.1%, p=0.021) were significant individual predictors of ΔMADRS (ηp^2=0.08, p=0.003 and ηp^2=0.051, p=0.021 respectively). When applied to the AUP patient group, a similar model predicted 19.0% (p=0.043) of the variance in ΔMADRS. In this model age predicted 9.7% (p=0.021) of the ΔMADRS, while none of the character dimension changes contributed significantly to the model.

The Pearson's correlation coefficients were: r=-0.185, p=0.054 between ΔRD and ΔMADRS in non-AUP patients and r=-0.377, p=0.003 in AUP patients; r=-0.301, p=0.001 between ΔSD and ΔMADRS in non-AUP and r=-0.249, p=0.058 in AUP patients; r=0.205, p=0.032 between ΔST and ΔMADRS in non-AUP patients and r=-0.119, p=0.368 in AUP patients. At baseline, correlations between age and SD, C, and ST were r=0.260 (p<0.001), r=0.203 (p=0.003), and r=0.134 (p=0.049) respectively. At 6 weeks correlations between age and SD, C, and ST were r=0.233 (p=0.002), r=0.206 (p=0.006), and r=0.193 (p=0.010) respectively.

5.3 Temperament and character profiles as predictors and the effect of harmful drinking on outcome of depression over two-year follow-up (III)

In Study III, the number of patients who dropped out was 65 (27%) at 6 weeks, 91 (38%) at 6 months, and 147 (61%) at 24 months. Of the dropouts the clinical treatment had been concluded in cooperation with the patients in 10 (11%) during

the first 6 months and in 28 (19%) cases before 24 months. There were no differences in the gender distribution or baseline MADRS scores between dropouts and completed patients. Baseline AUDIT scores were higher in the dropouts than among completed patients in the dropout analysis: at 6 months ($p<0.001$, t-test) and at 24 months ($p=0.006$). Dropped out patients had lower SD in the dropout analysis at 6 months (dropouts 117.9±18.3 vs. other patients 124.2±18.2, $p=0.02$ for t-test), but the difference was non-significant at 24 months ($p=0.09$). There was no statistically significant difference in LOCF MADRS scores between dropped out and other patients at 6-month dropout analysis ($p=0.2$), but the LOCF MADRS scores were higher in dropouts at 24 months (dropouts 12.9±8.9 vs. other patients 8.3±7.6, $p<0.001$ for t-test).

The results of the main analysis with the linear mixed effects model are presented in Table 8. The model predicted LOCF MADRS scores in the follow-up from 6 weeks to 6 months and to 24 months. Reward Dependence was the only statistically significant TCI-R dimension in predicting the outcome in the model. The estimate for this variable was negative, indicating higher values of RD being a predictor of steeper decline in MADRS scores across the 24-month follow-up. Time x AUP and Time x non-AUP interaction variables were significant predictors of the outcome in the model and the absolute value of the estimate was higher for Time x non-AUP indicating a steeper decline in MADRS scores over the follow-up in non-AUP patients.

Table 8. Predictors of depression outcome (LOCF MADRS scores across follow-up from 6 weeks to 6 months and to 24 months)[a]

Fixed effects	LOCF MADRS scores			
	Estimate[b]	SE	t	p
Intercept	20.07	10.04	2.00	0.049
NS at 6 weeks	0.04	0.03	1.16	0.25
HA at 6 weeks	0.06	0.04	1.70	0.09

RD at 6 weeks	**-0.11**	**0.04**	**-3.03**	**0.003**
P at 6 weeks	-0.03	0.03	-1.10	0.27
SD at 6 weeks	-0.06	0.04	-1.59	0.11
C at 6 weeks	0.02	0.04	0.56	0.58
ST at 6 weeks	0.05	0.03	1.49	0.14
Male gender	0.24	1.76	0.14	0.23
AUP	3.67	1.64	2.25	0.12
AUP x Male gender	-3.24	2.19	-1.48	0.14
AUP x Time	**-0.10**	**0.05**	**-1.98**	**0.0002**
non-AUP x Time	**-0.33**	**0.06**	**-3.75**	**0.0002**

-2 x log-likelihood = 3530 for the SAS input code and output results

[a]Results from the linear mixed effects model with temperament and character dimension scores, gender, AUP, and AUP x Gender and AUP x Time interactions as explanatory variables

[b]B for the temperament and character variables effect on the dependent variable

Abbreviations: LOCF = Last observation carried forward; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; P = Persistence; SD = Self-Directedness; C = Cooperativeness; ST = Self-Transcendence; MADRS = Montgomery-Åsberg Depression Rating Scale; AUP = alcohol use problems

Significant results are presented in bold face.

The LOCF data had a lower proportion of patients reaching response and remission in the 6-month and 24-month follow-up points compared to the raw data (Table 9.). The proportion of male patients and AUP patients declined in the raw data across the follow-up. The TCI-R scores at 6 weeks are presented in Tables 5 and 6.

There were significant correlations between RD and LOCF MADRS scores at 6 months (r=-0.32, p<0.001), HA and LOCF MADRS scores at 6 months (r=0.18, p=0.02), SD and LOCF MADRS scores at 6 months (r=-0.27, p<0.001), HA and LOCF MADRS scores at 24 months (r=0.26, p=0.001), and SD and LOCF MADRS scores at 24 months (r=-0.32, p<0.001).

Table 9. MADRS scores in raw data, LOCF data, and by patient subgroup and number of responders, patients in remission, and non-responders at baseline and follow-up

	Baseline	6 weeks	6 months	24 months
Raw data MADRS scores (mean±SD)	23.2±6.7; n=228	16.9±8.0; n=188	13.1±8.7; n=156	8.3±7.6; n=95
Response* (n, %)			69, 44%	64, 67%
Remission** (n, %)			49, 31%	50, 53%
LOCF data MADRS scores, n=188			13.6±8.5	10.6±8.5
Response* (n, %)			80, 43%	112, 60%
Remission** (n, %)			52, 28%	80, 43%
MADRS scores of patient subgroups (Raw data scores):				
non-AUP (mean±SD)	22.9±6.7 (n=136)	16.7±8.0 (n=123)	12.8±8.7 (n=105)	6.7±6.2 (n=66)
AUP (mean±SD)	23.7±6.7 (n=92)	17.2±8.1 (n=65)	13.7±8.7 (n=51)	12.0±9.2 (n=29)
Female (mean±SD)	22.3±6.8 (n=137)	15.7±7.8 (n=112)	11.6±8.2 (n=97)	7.1±6.6 (n=64)

Male (mean±SD)	24.6±6.3 (n=91)	18.6±8.0 (n=76)	15.6±9.1 (n=59)	10.8±8.9 (n=31)
proportion of men (n, %)	91, 40%	76, 40%	59, 38%	31, 33%
proportion of AUP patients (n, %)	92, 40%	65, 35%	51, 33%	29, 31%
Number of patients with increase in symptoms from baseline (n, %)			23, 15%	3, 3%

Abbreviations: AUP= Alcohol use problems; MADRS = Montgomery-Åsberg Depression Rating Scale; LOCF = last observation carried forward

*at least 50% MADRS score decline from baseline; **MADRS scores < 8

5.4 Association of temperament clusters with anxiety disorder comorbidity in depression (IV)

The two-step cluster analysis of the ODS patient cohort resulted in four clusters with different temperament profiles. These clusters were given descriptive labels according to the individual combination of different temperament dimension scores. The clusters found were: 1) Novelty seekers with high NS, n=56, (NS=119.4±9.0, HA=111.0±14.2, RD=103.3±13.5, P=98.0±15.5; mean±SD), 2) Persistent with low HA and high P, n=36, (NS=99.6±17.1, HA=87.3±11.0, RD=107.9±15.6, P=125.0±12.6), 3) Reserved with low NS, n=66, (NS=88.1±12.3, HA=119.9±11.5, RD=104.5±14.6, P=105.4±15.6), and 4) Wearied with high HA and low RD and P, n=58, (NS=95.7±10.4, HA=129.8±14.8, RD=84.7±14.3, P=82.4±15.3). The TCI-R dimension scores of the different temperament profiles are presented in Figure 7.

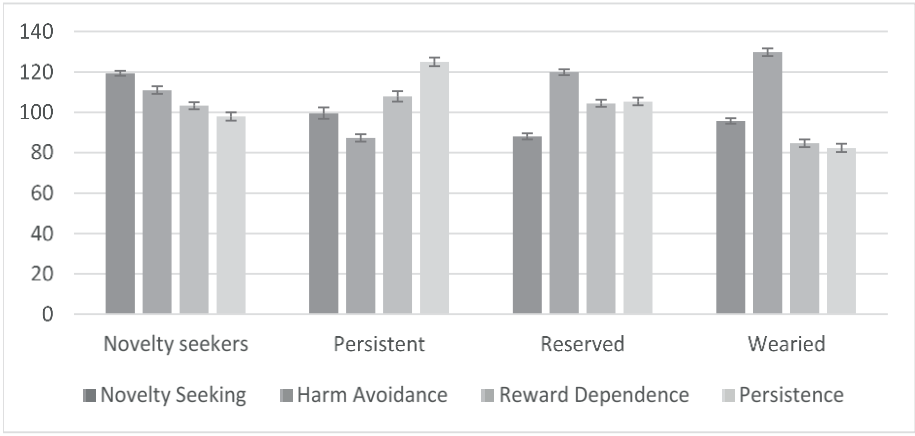

Figure 7 Temperament dimension (Mean±S.E.) scores of the four temperament clusters.

Wearied patients were younger than Persistent and Reserved patients, but there were no other significant differences in the clinical variables tested (gender, depression severity, alcohol use, use of antipsychotics or prescribed equivalent doses of antidepressants) between the clusters. Highest prevalence of GAD was found in Reserved (n=20, 31.7%), highest prevalence of SAD in Wearied (n=19, 34.5%), highest prevalence of PDA in Novelty seekers (n=28, 54.9%), and lowest overall prevalence of anxiety disorder comorbidities was found in Persistent patients. The chi-square values and p-values for the differences in clinical variables are presented in Table 10 and the chi-square values and p-values for the differences in anxiety disorders between the temperament clusters are presented in Table 11.

Table 10. Clinical characteristics and their differences between the four temperament clusters (Novelty seekers, Persistent, Reserved and Wearied)

	Clinical variables					
Temperament clusters	Age * (mean±SD)	Male gender (n, %)	Antipsychotics in use	Antidepressant dose (mean±SD)	AUDIT-C scores (mean±SD)	MADRS scores (mean±SD)
1. Novelty seekers (n=56, 26%**)	36.7±12.5	29, 51.8%	16, 28.6%	27.2±21.4	5.64 ±3.64	22.4±6.6
2. Persistent (n=36, 17%**)	42.5±12.2	12, 33.3%	7, 19.4%	25.2±18.7	4.31 ±3.43	23.1±7.7
3. Reserved (n=66, 30%**)	41.4±11.6	22, 33.3%	15, 22.7%	25.0±21.0	4.39 ±3.29	22.6±6.1
4. Wearied (n=58, 27%**)	34.8±11.4	25, 43.1%	22, 37.9%	32.4±19.2	4.93 ±3.24	24.5±5.4
χ^2		5.28	5.08			
p	**0.003**[1]	0.15[2]	0.166[2]	0.18[1]	0.16[1]	0.26[1]

Abbreviations: AUDIT-C = Alcohol use disorder identification test (questions 1–3); MADRS = Montgomery-Åsberg Depression Rating Scale

Percentages in clinical variables are proportions of the temperament clusters

*differences were significant between clusters 2 and 4, and between clusters 3 and 4 in Bonferroni analysis

**proportion of the whole patient sample

[1]for ANOVA between the temperament clusters

[2]for chi-square between the temperament clusters

Significant differences are presented in bold face

Table 11. Distributions of anxiety disorders and differences in these between the four temperament clusters (Novelty seekers, Persistent, Reserved and Wearied)

	Diagnoses		
Temperament clusters	PDA (n, %)	SAD (n, %)	GAD (n, %)
1. Novelty seekers (n=56, 26%*)	28, 54.9%	10, 19.6%	7, 13.7%
2. Persistent (n=36, 17%*)	5, 14.3%	1, 2.9%	8, 22.9%
3. Reserved (n=66, 30%*)	14, 22.2%	10, 15.9%	20, 31.7%
4. Wearied (n=58, 27%*)	22, 40.0%	19, 34.5%	6, 10.9%
χ^2	**20.81**	**14.57**	**9.67**
p	**<0.001**[1]	**0.002**[1]	**0.02**[1]

Abbreviations: PDA = Panic disorder and/or Agoraphobia; SAD = Social anxiety disorder; GAD = Generalized anxiety disorder

Percentages in diagnoses are proportions of the temperament clusters

*proportion of the whole patient sample

[1]for chi-square between the temperament clusters

Significant differences are presented in bold face

In the three types of models built to predict the anxiety disorders Novelty seekers had higher odds (odds ratio [OR]=3.28–3.52, p≤0.001) for PDA, Wearied had higher odds (OR=3.17–3.41, p=0.002–0.003) for SAD, and Reserved had higher odds (OR=2.53–2.60, p=0.009–0.01) for GAD compared to other patients. The results of these regression models are presented in Table 12.

Table 12. Likelihood of anxiety disorders (PDA, SAD and GAD) according to temperament. clusters in the logistic regression models

	PDA			SAD			GAD		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Model 1									
Temperament cluster*	3.28	1.67-6.41	0.001	3.17	1.49-6.76	0.003	2.60	1.27-5.33	0.009
Model 2									
Temperament cluster*	3.52	1.78-6.96	<0.001	3.19	1.47-6.90	0.003	2.53	1.23-5.21	0.01
Model 3									
Temperament cluster*	3.48	1.76-6.91	<0.001	3.41	1.55-7.49	0.002	2.55	1.24-5.27	0.01

Model 1: adjusted for gender and age

Model 2: adjusted for gender, age, and MADRS scores

Model 3: adjusted for gender, age, MADRS scores, and AUDIT-C scores

*Binominal variables: 1) Novelty seekers cluster vs. others explaining PDA, 2) Wearied cluster vs. others explaining SAD, and 3) Reserved cluster vs. others explaining GAD

Abbreviations: PDA = Panic disorder and/or agoraphobia; SAD = Social anxiety disorder; GAD = Generalized anxiety disorder; MADRS = Montgomery Åsberg Depression Rating Scale; AUDIT-C = Alcohol use disorder identification test (questions 1–3), OR = odds ratio, CI = confidence interval

6 DISCUSSION

6.1 Summary of the main results

In Study I we found three clusters with different temperament profiles. These clusters predicted depression outcome when age was controlled for. A model in which vegetative symptoms of depression at baseline was used as a predictor together with the temperament clusters and age explained the largest proportion of response to antidepressant treatment. (I)

Alcohol use problems (AUP) predicted high NS and low P and SD in GLMs adjusted for age, gender, and baseline severity of depression. In GLMs adjusted for age and gender, increase in RD (over 6-week follow-up) predicted a decline in MADRS specifically in the AUP group in contrast to patients without this comorbidity. The third main finding of the study was that after controlling for age and gender, increase in SD and decline in ST (over 6-week follow-up) predicted a decline in MADRS specifically in the non-AUP group in contrast to patients with marked alcohol use problems (AUP). (II)

The main finding in Study III was that better outcome of depression was predicted by high Reward Dependence (score at 6 weeks) in the follow-up from 6 weeks to 6 months and to 24 months. Alcohol use problems were associated with slower decline of MADRS scores in follow-up. (III)

In Study IV four clusters of patients with unique temperament profiles were identified. These clusters had different associations with anxiety disorder comorbidities. More specifically, panic disorder and/or agoraphobia were predicted by the Novelty seekers temperament, social anxiety disorder by Wearied temperament, and generalized anxiety disorder by Reserved temperament in this sample of diverse depressed patients in regression models adjusted for potential clinical confounding variables. (IV)

6.2 Temperament clusters and vegetative symptoms of depression as predictors of antidepressant response (I)

In Study I, although in one of the temperament clusters identified the difference in RD was not statistically significant, the cluster model indicates that the MDD patients in the DEPGEN patient sample could be divided into three clusters according to combinations of their temperament dimensions.

Patients with temperament profile with low NS, high HA, and low RD had the most modest response to antidepressant treatment, whereas patients with the opposite profile (HNS/LHA/(HRD)) had the best response and the level of response in patients with the third temperament profile with intermediate NS, high HA, and high RD was in between the two other clusters. These temperament profiles predicted response to antidepressive treatment when the patients' age was controlled for. Although the model predicted only less than one tenth of the response, these results suggest that temperament clusters are indeed a predictor of antidepressant treatment response.

Earlier studies have shown that high HA is associated with poorer outcome of depression and the finding of this study concurs well with those findings because the temperament clusters that were associated with poorer outcome had high HA (Kampman, Poutanen 2011). High NS could be associated with lower level of depressive symptomatology, but no conclusive evidence of this association is available in depressed populations (Kampman, Poutanen 2011, Farmer, Mahmood et al. 2003). The evidence of the associations between RD and depression has been inconsistent (de Winter, Wolterbeek et al. 2007, Farmer, Mahmood et al. 2003, Richter, Polak et al. 2003, Naito, Kijima et al. 2000). Arguably one possible explanation for these discrepancies could be that the complete profiles with different combinations of each temperament dimension would be more important in the context of depression response instead of NS or RD dimensions individually.

Vegetative symptoms of depression (cf. melancholic type of depression) have historically been associated with a more "endogenous" type of depression and more recently with seasonal affective disorder (Paykel 2008, Grimaldi, Partonen et al. 2009). Some evidence exists that vegetative symptoms of depression may be associated with early stages of depressive episode and expression of immunological mediators (Grimaldi, Partonen et al. 2009, Maes 1993, Wichers, Koek et al. 2005). In one study high level of vegetative symptoms was associated with poorer response to fluvoxamine (Higuchi, Sato et al. 2008a). The associations of vegetative symptoms

of depression and temperament clusters with depression outcome have not so far been studied. To analyze the possible modifying effect of vegetative symptoms on the association between temperament clusters and antidepressant response, the second model in Study I included temperament clusters and vegetative symptoms of depression both with age as predictors. This model predicted twice the proportion in the variance of antidepressant treatment response compared to the model that had temperament clusters as the sole predictor, along with age. However, the explanatory proportion of the temperament clusters was smaller and non-significant in this model. The increase in the explanatory proportion of the whole model when vegetative symptoms were added into the model as a predictor suggest that vegetative symptoms of depression are individually a marked predictor of antidepressant treatment outcome. Moreover, it is possible that the vegetative symptoms of depression mediate the effect of temperament clusters on the antidepressant treatment response because their individual explanatory proportion was smaller (and statistically non-significant) in the second model. However, the association between temperament and vegetative symptoms of depression would have to be established in further studies to reach that conclusion. Indeed, some data exists that high Reward Dependence combined with low Persistence is negatively associated with appetite loss and low energy (Grucza, Przybeck et al. 2003). Moreover, harm-avoidant individuals might be less likely to experience typical vegetative symptoms during episodes of clinical depression according to one study (Grucza, Przybeck et al. 2003).

An analysis predicting the temperament clusters with clinical variables was performed to acquire information about possible confounding variables to adjust the model used in the main analysis predicting depression outcome. This analysis resulted in only age being a marginally significant predictor of the temperament clusters and it was therefore important to adjust the models predicting the outcome of depression in the main analysis for age. However, age was not significant in predicting antidepressant treatment outcome in the regression models.

6.3 The effect of alcohol use problems on temperament and character profiles and antidepressive treatment response (II)

In the ODS cohort, patients without marked alcohol problems (non-AUP) had similar temperament profiles to earlier samples with MDD patients (Jylhä, Mantere et al. 2011, Perna, Vanni et al. 2014). At baseline patients with alcohol use problems (AUP) had higher NS, and lower P, SD, and C than non-AUP patients, a notion that resembles the earlier finding of differences between depressed patients with or without history of alcohol dependence (Rae, Joyce et al. 2002). These temperamental differences and characteristics of depressed patients with alcohol use problems could be reflected in clinical settings as tendencies to be more enthusiastic about trying new treatments (high NS) but also to have difficulties related to treatment adherence because of a lack of self-control, cooperation, and persistence.

6.3.1 Temperament dimensions

To analyze the association between alcohol use problems and temperament and character GLMs adjusted for gender, age, and baseline severity of depression were used to predict each TCI-R dimension score (at baseline and at 6 weeks) with AUP as explanatory variable. After controlling for other clinical variables AUP was an individually significant predictor of NS scores at baseline and suggested a trend close to significance at 6 weeks. In the GLMs predicting NS scores the severity of depression was not significant in predicting the scores. These findings in Study II are well in line with earlier knowledge of high NS being a trait-like characteristic increasing the risk of SUDs and highlight the role of high NS being a risk factor for SUDs regardless of depressive symptomatology (Sher, Bartholow et al. 2000).

The male patients' HA scores decreased significantly over the 6-week follow-up, which was an expected result as depression is known to increase the scores on that dimension (Kampman, Poutanen 2011). Surprisingly, female patients' HA scores did not decrease markedly during follow-up, which suggests that these patients' depression is associated with different disease mechanisms than those traditionally associated with MDD patients. It is possible that because of the more lenient inclusion criteria the ODS sample included greater numbers of patients with a differentiated depression spectrum disorder associated with female gender, family

history of SUDs, recurrent episodes of MDD, and greater psychiatric comorbidity (Davis, Frazier et al. 2007, Winokur, Coryell 1992). These patients' depressive symptomatology could be more associated with the reward mechanisms in the brain, possibly leading to reward-seeking behavior such as substance use and the permanently high levels of HA could predispose them to recurrence of depressive episodes (Kampman, Poutanen 2011).

Although temperament is considered to be reflective of relatively stable traits, depression is known to be associated with state dependent changes in HA and some changes in temperament and character have been associated with favorable outcome of depression recovery (Kampman, Poutanen 2011, Corruble, Duret et al. 2002). The GLMs predicting change in MADRS scores in 6-week follow-up with Δ-variables of the TCI-R dimensions aimed to analyze the associations between the possible state dependent alterations of temperament or character and response to antidepressive treatment. In the temperament model adjusted for age, gender, and AUP status, the change in RD was the only individually significant predictor of the antidepressive treatment response. Because the earlier data on the state dependency of RD in depression are inconsistent, we wanted to analyze whether the association could be a specific characteristic of depressed patients with marked alcohol use problems (de Winter, Wolterbeek et al. 2007, Farmer, Mahmood et al. 2003, Richter, Polak et al. 2003, Naito, Kijima et al. 2000). Therefore, similar GLMs predicting antidepressive treatment response were also applied separately to AUP and non-AUP patients. Indeed, the model was non-significant in predicting the outcome in non-AUP patients but predicted over one fourth of the variance in ΔMADRS in the AUP group. The finding that increase in RD correlated with decrease in MADRS scores in the correlation analysis together with the results in the GLMs suggests that increase in Reward Dependence is a predictor of antidepressive treatment response at 6 weeks in depressed patients with alcohol use problems. When considering earlier data these patients' depressive symptoms could be more related to physical and vegetative symptoms of depression (Grucza, Przybeck et al. 2003) and could be reflective of different functions of brain antireward mechanisms associated with noradrenergic systems, HPA-axis, and endogenous oxytocin (Bell, Nicholson et al. 2006, BuismanPijlman, Sumracki et al. 2014, Cloninger 1986, Koob, Le Moal 2008).

In the GLMs AUP was a significant predictor of Persistence (P) at 6 weeks and showed a trend towards significance in predicting baseline P when the clinical variables were controlled for in the model. This is in line with earlier data suggesting that low P is associated with SUDs in depressed patients (Evren, Evren et al. 2009, Rae, Joyce et al. 2002), and according to an earlier study means that these patients

could suffer from more profound loss of energy and appetite loss (Grucza, Przybeck et al. 2003).

6.3.2 Character dimensions

In line with earlier evidence the depressed patients with alcohol use problems in the ODS cohort had lower SD than patients without this comorbidity (Fernandez-Mondragon, Adan 2015). Self-Directedness is associated with similar traits (e.g. self-sufficiency, responsibility, reliability, and goal orientation) as the concept of locus of control and these traits are suggested to be associated with the functions in the dorsolateral and ventral prefrontal cortex, and the cingulate cortex (Declerck, Boone et al. 2006, Cloninger, Svrakic et al. 1993). Interestingly, the neuropathological changes in the brain due to excessive alcohol use are also found in these same brain regions (Harris, Jaffin et al. 2008). The finding of lower SD in depressed patients with alcohol use problems could thus be based on neuropathology (Harris, Jaffin et al. 2008, Bosco, Capozzi et al. 2014) and it is possible that excessive alcohol use causes low SD in the long term. However, reverse causality cannot be ruled out either.

There was a significant increase in the SD scores in non-AUP patients during the 6-week follow-up and this change was a significant predictor of the antidepressive treatment response at 6 weeks in this patient group. This finding is in line with earlier evidence suggesting that state dependent changes in SD are associated with depressive episodes (Nery, Hatch et al. 2009, Corruble, Duret et al. 2002). All patients in the ODS study received behavioral activation (BA) as psychosocial treatment (Bottonari, Roberts et al. 2008, Dimidjian, Hollon et al. 2006, Dobson, Hollon et al. 2008, Weinstock, Whisman 2007). This intervention includes techniques aimed at improving skills associated with higher SD and may be associated with an increase of SD in the non-AUP patients in this study. However, no increase in SD was observed in patients with marked alcohol use problems and no association between ΔSD and antidepressive treatment response was found in the GLM in this patient group. These results could suggest that depressed patients with alcohol use problems may benefit less from BA in the acute stage of treatment, possibly due to lower capacity in self-reflection and self-regulation (Bosco, Capozzi et al. 2014, Declerck, Boone et al. 2006, Harris, Jaffin et al. 2008).

Although, Cooperativeness scores were significantly lower in patients with alcohol use problems in the ODS cohort, other clinical variables (instead of the

patient group) explained C in the GLMs. These results of age being a predictor of C lends support to the hypothesis of character maturation (i.e. an increase in character scores during the aging process) (Cloninger, Svrakic et al. 1993). The most likely reason for the differences in the C scores between AUP and non-AUP is the unequal gender distribution between the groups because C is known to be generally higher in women and the non-AUP group had a higher proportion of female patients (Yamasue, Abe et al. 2008). The change in Cooperativeness was a non-significant predictor of antidepressive treatment response across 6-week follow-up in all patient groups, unlike the two other character dimensions. This means that alleviation of depressive symptoms at acute stages of treatment is more associated with changes in patients' tendencies in self-governing and spiritual affiliation than with their ability to cooperate (Cloninger, Svrakic et al. 1993).

Earlier studies have suggested that Self-Transcendence may be correlated with depressive symptoms, but other studies have reported non-significant or contradictory findings (Farmer, Seeley 2009, Nery, Hatch et al. 2009, Spittlehouse, Pearson et al. 2010, Richter, Polak et al. 2003). One possible explanation for these discrepancies is differences between different demographic areas (Farmer, Mahmood et al. 2003). Another explanation could be that the ODS sample may have included more patients with subclinical bipolar disorder, because high ST is found in patients with bipolar disorder (Zaninotto, Souery et al. 2015, Zaninotto, Solmi et al. 2016). In this study ST decreased in the non-AUP group during 6-week follow-up and the decrease in ST also predicted antidepressive treatment response in this patient group. These results suggest that higher levels of depressive symptoms are associated with higher ST in depressed patients in psychiatric secondary services.

6.4 Association of temperament and character profiles with depression outcome across two-year follow-up in patients with harmful drinking (III)

In contrast to some other studies the results of Studies II and III suggest that Reward Dependence is associated with acute stage antidepressive treatment response and more long-term outcome of depression across follow-up from 6 weeks to 6 and 24 months (Farmer, Seeley 2009, Corruble, Duret et al. 2002). The difference between the present results and the results in earlier studies could be explained by differences in the patient samples studied because patients with SUDs had been excluded earlier

but AUDs were highly prevalent in the ODS sample (Corruble, Duret et al. 2002, Farmer, Seeley 2009). The results in Study II showed that increase in RD during acute stage of antidepressive treatment predicts alleviation of depressive symptoms specifically in patients with marked alcohol use problems and the finding of high RD as a predictor of long-term outcome of depression in Study III is likely a characteristic of that same group of patients. In line with our results, one earlier study that did not exclude patients with SUDs found an association between low RD and current depressive symptoms (Nery, Hatch et al. 2009). The results of another earlier study suggested an association between lower levels in RD and specifically dual diagnosis (comorbidity of severe mental illness and substance use disorder) (Fernandez-Mondragon, Adan 2015). The finding of an association between high RD (at 6 weeks) and better outcome of depression together with the results in Study II may be explained by depression state-dependent alterations in brain reward pathway functions (i.e. dysfunctional reward processing, e.g. deficit in reinforcement learning or impaired ability to modify behavior as a function of positive reinforcement) in patients comorbid with SUD (Höflich, Michenthaler et al. 2019, Admon, Pizzagalli 2015, Koob, Le Moal 2008). These findings support a possible association between Reward Dependence and depression treatment outcome when alcohol use problems are taken into account.

In contrast to repeated earlier findings on the associations between depression and HA or SD, the scores in these TCI-R dimensions did not predict outcome of depression on a significant level in this study (Farmer, Seeley 2009, Kampman, Poutanen 2011, Asano, Baba et al. 2015). Because there are well documented associations between AUDs and 1) the development of more chronic courses of depressive symptomatology (Holzel, Harter et al. 2011) and 2) high HA and low SD (Fernandez-Mondragon, Adan 2015, Sher, Bartholow et al. 2000), it is possible that alcohol use problems are a mediator between the effect of these temperament and character factors on the outcome of depression. Moreover, it is plausible that lower capacity for organized problem solving (i.e. low SD) or the distress associated with behavioral inhibition (i.e. high HA) could predispose these individuals to developing alcohol use problems (Cloninger, Svrakic et al. 1993). Because AUP x time interaction had a significant effect on the MADRS scores in the linear mixed effects model, whereas HA and SD were non-significant predictors, the present results support the hypothesis that alcohol use problems mediate the effect of these temperament and character dimensions on the outcome of depression.

The interactions of AUP x time and non-AUP x time were highly significant in predicting the outcome of depression across the follow-up from 6 weeks to 6

months and 24 months. The estimate for AUP x time was negative and of higher absolute value compared to the estimate for non-AUP x time indicating inferior outcome of depression recovery in patients with alcohol use problems compared to patients without the comorbidity. This finding demonstrates the disruptive effect of alcohol use problems on the outcome of depression and is in line with earlier findings on the detrimental effect of AUDs on the course depression (Holzel, Harter et al. 2011, Burcusa, Iacono 2007). Temperament dimensions Novelty Seeking and Persistence and character dimensions Cooperativeness and Self-Transcendence were all non-significant predictors of the outcome of depression in the mixed effects model. These results suggest that in diverse populations with depression individual personality profile biased on one of these dimensions is not a predictor of the long-term outcome of depression when alcohol use problems are taken into account.

6.5 Association of temperament clusters with anxiety disorder comorbidity in depression (IV)

6.5.1 Temperament profile and Panic disorder

Panic disorder had the highest prevalence in the Novelty seekers having temperament profiles including highest NS, high HA, and intermediate levels in RD and P. According to Cloninger's original theory Novelty Seeking is associated with somatic anxiety and Harm Avoidance with cognitive anxiety (Cloninger 1986). Arguably panic attacks are a response to somatic anxiety and continuous concern about attacks to cognitive anxiety in the clinical picture of panic disorder. Finding the highest prevalence of PDA in the Novelty seekers cluster was an anticipated result because the patients in this cluster had presumably a high level of both types of anxiety according to Cloninger's theory reflected as having the highest NS and HA scores above the population norm (Cloninger 1986, Jylhä, Isometsä 2006). When possible confounding variables were controlled in the regression model, the Novelty seekers had three times as high odds for PDA compared to other patients, which suggests a strong association between this temperament profile and panic disorder. The majority of earlier studies have found no association between high NS and panic disorder in depressed patients and one study actually reported an inverse relation between the two (Ampollini, Marchesi et al. 1999, Ongur, Farabaugh et al. 2005, Kennedy, Schwab et al. 2001).

The explanation for finding a strong association between temperament profile with high NS and panic disorder in Study IV and not in earlier studies could be in the differences in the patient samples studied. Whereas earlier studies have excluded patients with SUDs (Kennedy, Schwab et al. 2001, Ongur, Farabaugh et al. 2005, Ampollini, Marchesi et al. 1999), the prevalence of alcohol use disorder in the ODS sample was high. Because patients with SUDs are likely to have higher NS scores (Howard, Kivlahan et al. 1997) and high predisposition for panic disorder (Zvolensky, Bernstein et al. 2006) the earlier studies may have excluded many patients with high NS and panic disorder, whereas the present study is likely to have included these patients, thus explaining the association found in this study. Moreover, the present study analyzed the association between the complete temperament profiles (combination of all temperament dimensions) and it is probable that the combination of high levels in NS and HA is important in explaining the high prevalence of panic disorder (and SAD) found in this group of depressed patients. Supporting this argument, a meta-analysis has suggested that panic disorder is associated with high HA (Kampman, Viikki et al. 2014).

Interoceptive functions (e.g. interoceptive conditioning and/or catastrophic misappraisals of bodily sensations) are central in the development of panic attacks and panic disorder according to some psychological theories (Craske, Waters 2005, Bouton, Mineka et al. 2001). High Novelty Seeking could be a moderator of the association between interoceptive functions and panic disorder hypothetically via the "histrionic" information processing style associated with high NS (Cloninger 1986), and because NS is associated with functions of the same brain regions (e.g. the right anterior cingulate cortex and the anterior/posterior insula) as interoception and panic disorder (Cui, Zhang et al. 2016, De Cristofaro, Sessarego et al. 1993, LeDoux, Pine 2016, Sugiura, Kawashima et al. 2000). Such a moderating effect would be in line with our finding of highest risk of PDA in patients with temperament profile including the highest NS (Novelty seekers) compared to patients with temperament profile with lower NS.

6.5.2 Temperament profile and Social anxiety disorder

Social anxiety disorder had the highest prevalence in Wearied subjects with temperament profiles including highest HA, low NS, RD, and P. With a control for possible confounding variables in the regression model, Wearied temperament showed three times as high odds for SAD compared to other profiles. This finding

was well in line with earlier evidence that highest levels of HA are associated with SAD in contrast to other anxiety disorders (Kampman, Viikki et al. 2014, Miettunen, Raevuori 2012) because Wearied temperament profile included the highest HA found in the clusters. As the severity of depression is also associated with higher scores in HA (Kampman, Poutanen 2011), these findings together suggest that the highest scores in HA are associated with more severe depression and SAD. According to Cloninger high HA is associated with behavioral inhibition and avoidance, as well as an obsessional information processing type (Cloninger 1987, Cloninger 1986). It is possible that the effect of high HA on SAD and depression is in part mediated by these traits of avoidant behavior and repetitive unconstructive thinking patterns (Kanter, Busch et al. 2008, Watkins 2008, Weinstock, Whisman 2007). Thus, the preceding findings could suggest that more profound cognitive bias towards repetitive and ruminative thinking patterns and avoidance are etiological factors more strongly associated with severe depression and SAD compared to other anxiety disorders. Moreover, the neurobiological correlates of high HA could resemble those of rumination and include heightened activity in the default mode network (Graham, Salimi-Khorshidi et al. 2013, Malhi, Byrow et al. 2015).

It has been suggested earlier that there is a higher order personality trait common to depressive and anxiety disorders and that other unique factors differentiate between the more specific separate disorders (Clark, Watson 1991, Craske, Waters 2005). Although the highest levels of HA could be associated especially with SAD and severe depression, in light of earlier evidence it is likely that high HA also presents more generally traits predisposing to psychopathology associated with mood and anxiety disorders (Kampman, Poutanen 2011, Kampman, Viikki et al. 2014, Miettunen, Raevuori 2012). Moreover, our results suggest that emotional detachment and low ambition (reflected as lower RD and P in the Wearied patients' temperament profile), compared with other features, could be important distinctive characteristics of this temperament profile that is associated specifically with higher risk for SAD.

6.5.3 Temperament profile and Generalized anxiety disorder

Generalized anxiety disorder had the highest prevalence in Reserved cluster and GAD was predicted by Reserved temperament with over two times as high odds compared to other patient groups in the regression models. Reserved patients had temperament profile with lowest NS scores, high HA and intermediate RD and P

(similar levels found in Finnish general population) (Jylhä, Isometsä 2006). These results are in line with earlier evidence reporting an association between GAD and high HA (Kampman, Viikki et al. 2014). Although no association between low NS and GAD has been found earlier (Ongur, Farabaugh et al. 2005, Piero 2010), our results suggest that a combination of high HA and low NS could be an important phenotype associated with GAD because Reserved patients' temperament profile included these characteristics and the profile had a higher risk for GAD. According to Cloninger's original theory Reserved patients would be less affected with "histrionic" or impulsive information processing, but instead could show a proclivity to slow or rigid decision-making, slow engagement in new interests or to be detail oriented due to low NS (Cloninger 1987, Cloninger 1986). It is possible that the difference in low/high NS found in the temperament profiles between Novelty seekers and Reserved is important in modulating the predisposition of these patients either to panic disorder or GAD when experienced together with other risk factors of developing psychopathology such as high HA (Cloninger 1987, Miettunen, Raevuori 2012).

6.5.4 Persistent temperament profile

The patients with Persistent temperament profile had the lowest prevalence of any anxiety disorders. Their temperament profile included lowest HA and highest P and the P scores in this patient group were even higher than those found earlier in a Finnish general population sample (Jylhä, Isometsä 2006). The finding of an association between temperament profile and a combination of low HA and high P and lower predisposition to anxiety disorder comorbidities was in line with earlier evidence suggesting that this profile together with character trait high SD is associated with positive emotionality and well-being (Cloninger, Bayon et al. 1998, Garcia 2011, Cloninger, Zohar et al. 2012). These results suggest that Persistent temperament profile is associated with less severe psychiatric symptomatology than are other temperament profiles.

6.6 Synthesis of the results of the four sub-studies (I-IV)

Together with earlier data the results in this study indicate that Reward Dependence is markedly associated with depression symptom alleviation in short-term follow-up

and low scores in RD are the most marked temperamental predictor (within the TCI-R instrument) of depression outcome, also in the long term (in two-year follow-up) in patient populations with diverse depressive symptomatology in psychiatric secondary services. Moreover, low RD seems to be a(n) (endo)phenotypical marker for depressive symptomatology with more marked treatment resistance and higher rate of comorbid substance use (Takahashi, Shirayama et al. 2013, Balestri, Porcelli et al. 2019). Whereas high HA could be more associated with the cognitive component of depressive symptomatology, RD could be more associated with the vegetative symptoms perhaps associated with neurobiological changes during depressive episode (Grucza, Przybeck et al. 2003). Together with high HA and low P, low RD presents Wearied temperament profile which is strongly associated with higher prevalence of comorbid anxiety disorders, especially social anxiety disorder.

6.7 Strengths and limitations

6.7.1 Strengths and methodological considerations

The approach of using TCI temperament clusters to predict the response to antidepressant treatment in MDD patients is novel. Some studies have been conducted using the individual dimensions of temperament as predictors, but only two earlier studies with general population samples have used combinations of high or low temperament traits to predict different clinical features. However, in these studies no cluster analysis methods have been used in classifying the temperament traits (Matsudaira, Kitamura 2006, Grucza, Przybeck et al. 2003). In this study the possible association between temperament and vegetative symptoms of depression was studied as a novel focus. This was done by separating the vegetative symptoms from the other symptom scales of depression (dysphoria and retardation), which was based on the study by Suzuki et al. 2005 (Suzuki, Aoshima et al. 2005). (I)

Studies regarding the differences in temperament and character dimensions between depressed patients with comorbid substance use and depressed patients without this comorbidity are limited (Rae, Joyce et al. 2002, Fernandez-Mondragon, Adan 2015). In Study II differences in TCI-R scores at baseline and after 6 weeks of treatment between these two groups were explored in a sample with larger numbers of patients than in the earlier study (Fernandez-Mondragon, Adan 2015) and the

prospective design of Study II provided information about different phenotypes of these disorders with a novel method. (II)

The associations between different temperament and character dimensions and depression recovery have been widely studied, but the associations between changes in these dimensions and antidepressive treatment outcome is a less studied subject although some findings have been reported (Corruble, Duret et al. 2002). In Study II the focus was particularly on the possible interactive effects of AUP with temperament and character change on antidepressive treatment response as a novel focus. (II)

In Study III a mixed effects multivariate model was used to analyze the factors predicting the outcome of depression (MADRS scores) across three different time-points (at 6 weeks, 6 months, and 24 months). This statistical method made it possible to fit individual-specific slope and intercept terms and to achieve greater precision in model fitting and parameter estimation than in earlier studies with a multiple model approach. (III)

Because the average duration of depressive episodes is 6 months, the follow-up period up to 6 months is an appropriate juncture to assess response to antidepressive treatment, whereas a follow-up period up to 24 months is likely to reflect the long-term outcome considerably better, also including relapses and recurrences of depressive episodes (Kupfer 1991, Solomon, Keller et al. 1997). Therefore it was important to study the outcome across both stretches of time in Study III to analyze the predictors of depression recovery more comprehensively (Solomon, Keller et al. 1997). However, it is possible that traits associated with response to treatment could be different from traits predisposing to recurrence of episodes and such a hypothesis could be tested in future studies in naturalistic samples (Farmer, Seeley 2009). (III)

The cluster model yielded four different combinations of the four temperament dimensions. Such a method arguably provides profiles that reflect a more comprehensive combinations of individual temperament-oriented behaviors in patients (Miettunen, Raevuori 2012). There are only few earlier studies in which more comprehensive temperament profiles have been analyzed in the context of psychopathology and to the best of our knowledge there are no earlier studies predicting anxiety disorder comorbidity with the temperament profiles provided by cluster analysis (Matsudaira, Kitamura 2006, Grucza, Przybeck et al. 2003). (IV)

6.7.2 Limitations

In the studies within the ODS cohort (II-IV) the 'real-life' setting, broad inclusion criteria, and few exclusion criteria posed some challenges and limitations. However, this broad inclusion approach provided results of high clinical relevance and generalizability. The studied cohort comprised diverse patients with at least moderate depressive symptomatology with marked comorbidity and recurrent MDD episodes, however, a vast majority of patients had a diagnosis of MDD. Some of the patients studied used other substances besides alcohol, which may have affected the results in this study on the effects of alcohol use. Although the use of other substances was infrequent and monitored with MINI as well as a question of use of other substances during the prior year, no data was collected on the type of substances used, nor were any biological samples studied to verify the accuracy of the self-reports. The prescribed psychopharmacological medications were diverse, but most of the patients were prescribed either SSRI or SNRI. The clinical efficacy of the prescribed medication was evaluated by a psychiatrist (and changed if necessary) and adherence to medical treatment was monitored. (II-IV)

We observed the anticipated uneven gender distributions between the non-AUP and AUP groups. Because of this, however, multivariate analyses as well as gender-wise divisions were required in addition to bivariate comparisons in analyzing the patients' temperamental differences. These multiple statistical analyses could lead to type 1 errors as Bonferroni correction (or equivalent) was not used. However, the bivariate analyses were only exploratory in nature and the final interpretation of the results was made according to the multivariate analysis. (II)

In Study III there was marked dropout, especially by the 24-month follow-up, which necessitated data imputation for the main analysis. The method of last observation carried forward was considered suitable in the follow-up with multiple measurement points. Because the naturalistic study setting allowed patients to continue in the study even if they had failed to attend at some earlier point, the risk that the LOCF protocol would have markedly influenced the results study by not detecting relapses in patients was considered low. (III)

The lack of non-depressed controls in Study IV limits the generalizability of these results outside depressed populations, i.e. these temperament clusters may only be a characteristic of depressed patients. Because of the high level of alcohol use problem comorbidities in the ODS sample the results may be applicable only to depressed populations in which patients with SUD comorbidities are not excluded. Moreover, the temperament profiles were assessed when the patients displayed depressive

symptoms, which is likely to have resulted in higher HA scores in the studied population (Kampman, Poutanen 2011). However, depression severity was controlled for in the regression models to avoid the bias of higher risk of anxiety disorders found in more severely depressed patients. (IV)

7 CONCLUSIONS AND CLINICAL IMPLICATIONS

1. The vegetative symptoms of depression together with temperament profiles and age were significant predictors of antidepressant treatment response. The effect of temperament profile alone was modest but, combined with vegetative symptoms of depression, their explanatory power was more marked. These findings suggest that the association between temperament profile and antidepressive treatment outcome could be mediated in part by the vegetative symptoms of depression and that there could be an association between these two in the biological background of MDD. (I)

2. In Study I MDD patients could be divided into distinct temperament clusters with different severity of depression and outcomes of antidepressant treatment. In practice this means that temperament profiles could differentiate between groupings of MDD patients with different outcomes for antidepressant treatment. (I)

3. Depressed patients with alcohol use problems had lower Self-Directedness and Persistence and higher Novelty Seeking than did depressed patients without the comorbidity. In clinical practice, this difference in temperament and character profiles could be reflected as depressed patients with alcohol use problems being more enthusiastic about trying new treatments, but less adherent to treatment. (II)

4. Changes in Reward Dependence and lower Self-Directedness in AUP patients could reflect differences in the biological mechanisms associated with depressive symptomatology between patients with alcohol use problems and those without. Over acute treatment duration, the increase in Self-Directedness and decrease in Self-Transcendence were associated with alleviation of depression in depressed patients without marked alcohol use problems. In contrast, no changes were observed in any character dimensions in patients with alcohol use problems suggesting that these patients may benefit less from behavioral activation therapy at the acute stage (0 to 6 weeks) of treatment. (II)

5. High Reward Dependence was associated with better anti-depressive treatment outcome in two-year follow-up, which is possibly a characteristic of depressed patients with alcohol use problems. Harm Avoidance and Self-Directedness were not predictors of depression outcome when alcohol use problems were controlled for. (III)

6. Temperament clusters with unique dimensional profiles were specifically associated with different anxiety disorders in the depressed patients of Study IV. More specifically, Novelty seekers temperament was associated with panic disorder, Reserved with generalized anxiety disorder, Wearied with social anxiety disorder, and Persistent with lower risk of anxiety disorder comorbidities. The results in Study IV suggest that TCI-R could offer a valuable tool for predicting the risk of anxiety disorders in diverse depressed patients. (IV)

7.1 Implications for future research

In Study I the vegetative symptoms of depression together with temperament clusters were a marked predictor of depression outcome at 6 weeks. The follow-up of 6 weeks can be considered short for analyzing outcome of MDE and studies with 6-month follow-up might yield results with more significant clinical implications. Another interesting line of study would be to analyze whether vegetative symptoms of depression are associated with depression recovery in patients in some specific temperament cluster.

In Studies II and III increase in RD at early stages of antidepressive treatment as well as high RD at 6 weeks were associated with positive outcome in depression recovery over 2-year follow-up. This association between Reward Dependence and depression outcome could be a characteristic of depressed population with prevalent alcohol use problems and this finding should be confirmed in other studies with naturalistic samples controlling for substance use. Future studies could also analyze if increase in RD is associated with depression recovery in patients with some specific temperament profile. BA and MI were used as psychosocial interventions in the treatment of the patients in ODS cohort and one interesting study subject in future could be to analyze whether increase in RD modifies the effect of these interventions on depression recovery.

It is possible that the temperament clusters found in Study IV reflect endophenotypes predisposing to different disorders, 1) because temperament

presents relatively stable traits and 2) because the temperament clusters were associated with different disorders. The temperament clusters could be more closely associated with the biological background of psychiatric symptoms than with categorical diagnoses or separate temperament traits and could help in the search for biomarkers for psychopathology (Service, Verweij et al. 2012). Testing of the possible associations between temperament clusters and candidate genes of anxiety disorders would therefore be interesting to perform in further studies (Sharma, Powers et al. 2016).

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A Cluster Model of Temperament as an Indicator of Antidepressant Response and Symptom Severity in Major Depression

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Objective Not enough is known about which patients suffering from major depressive disorder benefit from antidepressant drug treatment. Individual temperament is relatively stable over a person's lifespan and is thought to be largely biologically predefined. We assessed how temperament profiles are related to depression and predict the efficacy of antidepressant treatment.

Methods We recruited one hundred Finnish outpatients (aged 19 to 72) suffering from major depressive disorder, of whom 86 completed the 6-week study. We assessed their temperament features with the Temperament and Character Inventory and used cluster analysis to determine the patient's temperament profile. We also categorized the patients according to the vegetative symptoms of major depressive disorder.

Results There was an association between skewed temperament profile and severity of major depressive disorder, but the temperament profiles alone did not predict antidepressant treatment response. Those with higher baseline vegetative symptoms score had modest treatment response. Our model with baseline Montgomery Åsberg Depression Rating Scale (MADRS) vegetative symptoms, age and temperament clusters as explanatory variables explained 20% of the variance in the endpoint MADRS scores.

Conclusion The temperament clusters were associated both with severity of depression and antidepressive treatment response of depression. The effect of the temperament profile alone was modest but, combined with vegetative symptoms of depression, their explanatory power was more marked suggesting that there could be an association of these two in the biological basis of MDD.

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Key Words Depressive disorder, Temperament, TCI, Antidepressive agents, Treatment response.

INTRODUCTION

According to the psychobiological model of temperament and character[1] the human temperament can be divided into four different independent dimensions and character into three different dimensions. The temperamental features are: 1) the behavior in relation to new or pleasure-producing stimuli (novelty seeking, NS), 2) behavioral inhibition in relation to issues which may lead to negative consequences (harm avoidance, HA), 3) continuing of behavior that has earlier been successful in the hope of reward (reward dependence, RD), and the tendency to maintain certain behavior despite frustration (persistence, P).[1] These temperament dimensions are suggested to be connected with central neurotransmitter circuits in the central nervous system: dopamine (novelty seeking), serotonin (harm avoidance) and norepinephrine (reward dependence).[2] The three dimensions of character mature in adulthood and influence personal and social effectiveness by insight learning about self-concepts. Self-concepts vary according to the extent to which a person identifies the self as 1) an autonomous individual (self-directedness, SD), 2) an integral part of humanity (cooperativeness, C), and 3) an integral part of the universe as a whole (self-transcendence, ST).[1]

The Temperament and Character Inventory (TCI) has been

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used in general population studies and in studies including patients with major depressive disorder (MDD) to assess how different temperament dimensions are associated with this disorder.[1] HA has reportedly been higher in MDD patients than in general population[3-9] and has been state dependent in MDD.[5,6] HA has also been associated with depressive symptoms in general population.[10-12] HA, RD and NS have been found to have trait-like characteristics that are related to the familial occurrence of depression.[4] High HA has been reported to predict poor treatment outcome.[8,13-15]

HA also seems to have a trait-like characteristic, reflecting genetic susceptibility in depression prone subjects.[4,16] It seems that HA is both a state- and trait-dependent variable in MDD.[17] However, one study using the Hospital Anxiety and Depression Scale (HAD), which excludes somatic symptoms, found no association between HA and MDD.[18] This finding may suggest that HA is connected specifically to the somatic component of MDD. The contribution of other temperament dimensions in MDD is somewhat controversial or limited. Low RD may be associated with MDD and depressive symptoms in general population,[4] but the results are unequivocal.[10,19] NS seems to be state dependent in MDD and altogether lower in MDD patients.[4,11] However, high NS has been associated with history of suicide attempts in general population.[20] In one study P was a state marker in depression.[17]

In a study by Grucza et al.[20] different combinations of temperament dimensions were associated with different depressive symptoms. It has been proposed that the symptoms of MDD consist of clusters, which are linked to distinct genetic mechanisms which when combined in one individual, can lead to a diagnosable psychopathology.[21] Suzuki et al.[22] proposed a three-factor model of the MADRS to differentiate the vegetative symptoms (somatic symptoms) observed in a patient group. This three-factor model has been used in some studies with MDD patient samples.[23-25] It has been proposed that the vegetative symptoms are connected to enhanced expression of 5HT2A receptors.[25] We found no studies addressing the association of temperament and vegetative symptoms of MDD. The present study analyzes if temperament profiles in association with vegetative symptoms explain the antidepressant treatment response in MDD patients and if the severity of depression is associated with current temperament clusters.

METHODS

A hundred Finnish outpatients were recruited from secondary outpatient services, primary health care and by newspaper advertisements during the years 2002−2006 in the area of Tampere in southern Finland. The study was approved by the local Human Subjects Review Committee and subjects participated having given informed, voluntary, written consent. The recruitment resulted in 41 female and 59 male outpatients, aged 19−72 yrs (mean 40.7 years, SD±14.0). Patients met the criteria for major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). All patients were diagnosed by a psychiatrist and the severity of their depression was evaluated with the Montgomery-Åsberg Depression Rating Scale (MADRS). Those patients who scored 20 or higher at baseline MADRS were included in the study. Patients with severe somatic illness or medication affecting their mood, other significant psychiatric disorders (bipolar illness, psychosis or severe personality disorders) or patients with alcohol or substance abuse were excluded from the study. Eighty-six patients completed the entire study according to the protocol and were included in the final analysis.[26] Study data was collected on three occasions. At the first visit basic sociodemographic data was collected: gender, age, marital status, education, workplace before the sick leave, somatic illnesses and their medications, other psychiatric disorders, and possible use of psychotrophic medications. The baseline MADRS form was scored and the patients completed the temperament section of the TCI questionnaire to assess the temperament profile.[1] All patients were prescribed either citalopram, fluoxetine or paroxetine. Anxiolytics and sedative hypnotics as adjuvant treatment and other medication for concomitant general medical conditions were allowed. At the second visit, three weeks after initiation of treatment, patients' adherence to treatment and the dosage of the medications were checked. Compliance was evaluated by a medication diary kept by the patient. Treatment compliance was deemed sufficient if the patient had taken the medication on at least 80% of the days in the study period. At the third visit, six weeks after the initiation, patients' adherence was monitored again and the MADRS and TCI forms were completed again (endpoint data). In the case of possible dropouts the necessary patient information on the reasons for dropout was also collected. The temperament profiles were determined from the baseline TCI data. The vegetative symptoms were assessed as the sum of questions three to five in the MADRS.[22] These are impaired sleep, impaired appetite, and inner tension.

Statistical methods

A two-step cluster analysis was used for the definition of the patient's temperament profile. In our cluster model, we decided to use three temperament dimensions, NS, HA and RD with their baseline scores. In the statistical analysis the patients were divided into three clusters.

The differences in continuous variables (MADRS total score,

MADRS factor scores and age) between the clusters were calculated with ANOVA. The difference in MADRS change between low and high vegetative symptom groups was analyzed with t-test. Differences between grouping variables were calculated with χ^2-statistics. Non-parametric tests were used in comparisons in ordinal variables between different clusters (used medications, patient compliance). Pearson's correlation coefficients were calculated between MADRS total score and vegetative symptom score, both at baseline and endpoint.

In the multivariate analysis all variables included in the study and likely to have an impact on either depression severity or treatment response were used in the models. The effect of background variables on clusters was analyzed with a multinominal logistic regression model. Gender, age, severity of depression, antidepressant taken and dose, subjective adherence to treatment, and earlier depression episode were used as explanatory variables. A linear regression model (ANCOVA) was used for testing the effects of temperament clusters and other variables on MADRS endpoint scores. The first model included temperament clusters and age, and the second model temperament clusters, age and the MADRS vegetative symptoms (questions 3–5) at baseline as explanatory variables. All analyses were performed with SPSS for Windows software (version 17.0).

RESULTS

The cluster analysis resulted in the following clusters: LNS/HHA/LRD, INS/HHA/HRD and HNS/LHA/(HRD) with H indicating high level, L low level and I intermediate level on the temperament dimensions. In the third cluster RD did not reach statistical significance in the clustering model. In the first cluster we discovered the most robust slope in the NS and HA at baseline. In the second cluster there were elevated points in HA. The results of the cluster analysis and MADRS scores in each cluster are presented in Table 1.

There were no differences in the distributions of gender between the clusters (p=0.23, chi-square test). The patients in cluster 1 were older than in other clusters (age mean±SD, cluster 1=45.9±11.4, cluster 2=37.4±14.4, cluster 3=38.2±15.3; p=0.03, ANOVA). There was no difference between the clusters in the dosages of the medications taken in weeks one to three (p=0.48, Kruskal Wallis test), nor in compliance to treatment (p=0.69). Gender, severity of depression, antidepressant taken and dose, adherence to treatment, and earlier depression episode had no effect on the clusters in the multinominal regression model. Age of the patients had a marginal effect on clusters (p=0.051) in the multinominal regression model.

The correlations between MADRS vegetative symptom score with MADRS total score were at baseline 0.73, (p<0.001) and at endpoint 0.76, (p<0.001). The MADRS vegetative symptom score at baseline had a moderate correlation with MADRS endpoint scores (r=0.38, p<0.001), and a non-significant correlation with MADRS score change (r=0.13, p=0.26). We also analyzed the MADRS score change between patients with low (1–7, n=50) and high (8 or more, n=48) vegetative symptoms. The difference was close to significant [MADRS

Table 1. Results of the cluster analysis. All scores except response percentages are indicated as mean±SD

Cluster	LNS/HHA/LRD, N=33	INS/HHA/HRD, N=35	HNS/LHA/(HRD), N=30
TCI baseline score			
NS	13.9±5.2	19.6±7.1	25.7±4.9
HA	26.8±6.1	27.2±3.6	16.0±4.2
RD	11.8±2.2	18.2±2.5	16.6±3.6
Baseline MADRS*	28.3±6.1	27.3±5.7	25.0±4.4
Factor 1 (dysphoria)	8.5±2.6	7.8±2.2	7.4±1.4
Factor 2 (retardation)	11.7±2.2	12.1±2.7	11.0±2.9
Factor 3 (vegetative symptoms)	7.8±3.1	7.4±2.8	6.4±2.7
Endpoint MADRS**	14.1±9.1	13.5±8.3	8.3±5.5
Factor 1 (dysphoria)	3.7±3.2	3.9±2.7	2.5±1.9
Factor 2 (retardation)*****	6.3±4.5	6.0±3.7	3.4±3.0
Factor 3 (vegetative symptoms)	3.5±2.3	3.7±2.9	2.4±1.9
MADRS score change***	14.2±7.4	14.3±8.0	16.7±6.0
Response (percentage decline in MADRS)****	51.6%	51.9%	66.7%

*p=0.05 between groups (ANOVA), **p=0.01 between groups (ANOVA), ***p=0.36 between groups (ANOVA), ****p=0.04 between groups (ANOVA), *****p=0.01 between groups (ANOVA). TCI: Temperament and Character Inventory, MADRS: Montgomery-Åsberg Depression Rating Scale, NS: novelty seeking, HA: harm avoidance, RD: reward dependence, with H indicating high level, L low level and I intermediate level on the temperament dimensions

change, mean (±SD), low symptoms=13.5 (±5.5), high symptoms=16.6 (±8.5), p=0.052, t-test]. There were no differences in the MADRS vegetative symptom score at baseline or at endpoint between the different clusters (p=0.17, baseline; p=0.14, endpoint, ANOVA). There was a non-significant correlation between baseline MADRS dysphoria symptoms and MADRS score change (r=0.17, p=0.11). MADRS endpoint scores were used as the outcome variable in two linear regression models. In the first model age and temperament clusters were used as explaining variables. This model explained 10% of the variance in the MADRS endpoint scores (p=0.04; power 0.69). The clusters explained 9% (p=0.02), and age explained 1% (p=0.36). In the second model, baseline MADRS vegetative symptoms, age and temperament clusters were used as explanatory variables. This model explained 20% of the variance in the MADRS endpoint scores (p=0.001; power 0.96 for the complete model). In this model the baseline vegetative symptoms explained 12% (p=0.001), age 0.2% (p=0.70) and temperament clusters 5% (p=0.12). Using the delta scores of MADRS as an outcome variable, and age and temperament clusters as explanatory variables (first model), and vegetative symptoms, age and temperament clusters as explanatory variables (second model) resulted in non-significant models (first model: ηp^2=0.085, p=0.061, power=0.61; second model: ηp^2= 0.096, p=0.087, power=0.60).

DISCUSSION

Our main hypothesis was that temperament clusters in patients with MDD explain the treatment response. In practice this means that different temperament profiles could function as a classifying factor and that MDD patients could be divided into different groups with different outcomes for antidepressant treatment. In our study we used primarily the MADRS endpoint scores as an outcome variable in the multivariate analyses. Using the delta scores of MADRS as an outcome variable resulted in non-significant models although there was a trend towards a better response in patients with high vegetative symptoms. The present results suggest that the combined effect of vegetative symptoms and temperament clusters is important in relation to the depression treatment outcome when measured as post-treatment symptoms. However, these factors showed a non-significant effect when predicting the change in depression scores during treatment. This finding may be due to both the temperament clusters and pretreatment vegetative symptoms representing depressive traits less connected with the magnitude of symptom alleviation during treatment.

The approach of using TCI temperament clusters for predicting the response to antidepressant treatment in MDD patients is novel. In several studies individual dimensions of temperament have been used as precursors. Two earlier studies with general population samples have used combinations of high or low temperament traits for predicting different clinical features, but in these studies no cluster analysis method was used in classifying the temperament traits.[18,20] This study did not include the character dimensions of the TCI (SD, C, ST) in the explanatory model. Adding the character traits to the predictors in the statistical model might have increased its predictive value regarding antidepressant response, since many studies have demonstrated that SD exhibits a state/trait marker in depression.[9,27,28]

There were some limitations concerning our patient sample and study setting. In contrast to some earlier studies, our patient sample comprised solely outpatients. This may have resulted in lower intensity of symptoms as reflected by the MADRS scores. Temperament profiles could have had more explanatory power if the patient sample had included inpatients with more severe depression. The patients were deemed compliant with medication if they took the prescribed medication at least 80% of the time, which can be regarded as a moderate level of treatment compliance, and the data were collected from patient reports, which in some cases may produce unreliable results. Nor did the patients receive any specific psychological treatment during the study, but were treated in a standard secondary outpatient setting.

As the relationship between temperament and vegetative symptoms of depression has not previously been studied, a post-hoc analysis with vegetative symptoms was performed in this study. This was done by separating the vegetative symptoms from the other symptoms of depression (dysphoria and retardation) which was based on the study by Suzuki et al.[22] It has been proposed that the vegetative symptoms are connected to enhanced expression of 5-HT2A receptors.[25]

To assess patients' temperament profiles we used Cloninger's TCI, which has been widely used, validated and shown to be reliable in studies on general population and MDD patients.[1] Temperament profiles were determined by clustering the distributions in the three temperament dimensions. Due to the limited sample size, the number of clusters was determined as three in the analysis to yield groups of reasonable size. The clustering method was able to differentiate between the three combinations of temperament traits, although in the third cluster the difference on the dimension RD did not reach statistical significance. It has been suggested that high RD correlates negatively with depressive symptoms, but the evidence is contradictory.[3,4,9,10] The clusters differed on the dimension NS as it was low in cluster one, intermediate in cluster two and high in cluster three. The third cluster (HNS/LHA/HRD) probably reflects more impulsive depression, and diverges substan-

tially from the typical temperament profile of an MDD patient, and in this study from the other two temperament clusters. This may explain why this subgroup of patients recovered better from the retardation symptoms than did the other patients. In addition, this group showed a higher percentage of MADRS changes. This difference in response could be due to the predictive effect of HA on MDD remission shown in our earlier report.[29] In the first cluster we discovered the most distinct sloping in the distribution of the NS and HA dimensions at baseline. According to earlier reports the subgroup in this cluster has an increased risk for MDD and their depression is more disease-like.[4-6,9] NS has been negatively associated with depressive mood state and tends to be at a low level in MDD patients.[4] The clusters might thus reflect an underlying factor explaining clinically different symptoms profiles and course of depression.

In our study the temperament clusters were associated with both baseline and endpoint depressive symptoms and with the treatment response. The findings suggested that depression was most severe and difficult to treat in cluster one patients. In clusters one and two, in which HA scores were high, the response in percentage decline of MADRS scores was lower than in cluster three. These findings concur with those of earlier studies on the association between HA and depression.[4,5,7-9,15,30]

Although the depression vegetative symptom score is only a subscale of MADRS, it may be considered a separate dimension in depression symptomatology.[22] MADRS total scores and vegetative symptoms showed a strong correlation at both baseline and endpoint. However, the correlation between MADRS endpoint total score and baseline vegetative symptom score was much lower, suggesting that the vegetative symptoms are a separate entity within depressive symptomatology.[22] Therefore we considered it justified to study the impact of baseline vegetative symptoms on total symptoms at endpoint.

In the linear regression models our aim was to predict the treatment response in MDD patients. The first model was designed to reveal the impact of temperament clusters on treatment outcome. When patient's age was also taken into account as an explanatory variable, the temperament clusters had only modest explanatory power. Age as such did not function as an explaining variable in this model at a significant level. In the second model we wanted to ascertain if there was an interaction with temperament clusters and vegetative symptoms of MDD. Therefore we added the vegetative symptom scores to the model as an explanatory variable. In this model, the vegetative symptoms explained about twice as much as the clusters of the variance of endpoint MADRS scores. However, the whole model explained as much as one fifth of the variance in response to SSRI treatment. The role of the interaction between temperament clusters and vegetative symptoms on treatment result has to be interpreted cautiously, as the impact of clusters on treatment response in the final model was marginal. It seems that the vegetative symptoms of depression, in addition to a certain temperament profile, is a marked predictor for antidepressive treatment outcome. It is, however, possible that the vegetative symptoms alone have a more marked impact in both severity and response of depression compared to temperament. Even though the differences between the clusters in depression severity were marginal, our findings suggest an association between skewed temperament profile and severity of MDD. It is possible that the temperament profile can function as a predisposing factor to depression or have an impact on the clinical profile and course of depression.

In conclusion our study showed that MDD patients could be divided into different temperament clusters with different severity and outcomes of antidepressant treatment. The vegetative symptoms of depression combined with temperament profiles and age predicted antidepressant treatment response. The effect of the temperament profile alone was modest but, combined with vegetative symptoms of depression their explanatory power was more marked, suggesting that there could be an association between these two in the biological basis of MDD.

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Temperament and character profiles associated with depression and treatment response in patients with or without comorbid substance abuse

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ABSTRACT

There is limited knowledge on the relationship between temperament and character profiles and substance abuse comorbidity in depressed patients. We recruited 127 depressed patients without alcohol use problems (non-AUP) and 89 depressed patients with alcohol use problems (AUP). We assessed all patients using the Temperament and Character Inventory (TCI-R) at baseline and after 6 weeks of treatment. Using univariate general linear models (GLMs), we analyzed differences in TCI-R between AUP and non-AUP. GLMs were also used in analyzing the associations between TCI-R changes and antidepressive treatment responses measured with changes in Montgomery Åsberg Depression Rating Scale score (ΔMADRS). Alcohol use explained independently significant proportions of the variation in Novelty Seeking, Self-Directedness, and Persistence. Reward Dependence score change explained 14.1% of the ΔMADRS in AUP, but was non-significant in non-AUP. Character score changes in Self-Directedness and Self-Transcendence explained together 14.1% of ΔMADRS in non-AUP, whereas they were all non-significant in AUP. AUP compared with non-AUP patients had lower Self-Directedness and Persistence and higher Novelty Seeking scores. Detected changes in Reward Dependence and lower Self-Directedness in AUP patients could be reflective of different biological mechanisms associated with depressive symptomatology in alcohol abuse. Changes in character are associated with acute treatment response in non-AUP.

1. Introduction

Because of the extensive overlapping of different psychiatric disorders, the need for new integrative hypotheses regarding psychopathology has been proposed. It is argued that temperament could serve as a basis for this kind of integrative model (Clark, 2005). Depressive and alcohol-related disorders represent a major burden of disease in western countries (Ferrari et al., 2013; Laramee et al., 2013). Comorbidity with other psychiatric and substance use disorders (SUD) in patients with major depression (MDD) is marked, and one fourth suffer from comorbid alcohol use disorder (Davis et al., 2006; Melartin et al., 2002). Individuals with MDD and concurrent SUD are more likely than those without SUD to be younger, male, and either divorced or never married (Davis et al., 2008). Familial and genetic factors seem to have an effect on the co-occurrence of MDD and SUD, with reciprocal causation of the two supported by a large twin-pair study (Lyons et al., 2006).

According to the psychobiological model of temperament (Cloninger et al., 1993), human temperament is largely genetically determined and forms in early childhood. It consists of four different dimensions, including 1) Novelty Seeking (NS; initiation or activation of appetitive behavior in response to novelty), 2) Harm Avoidance (HA; inhibition of behavior in response to signs of punishment), 3) Reward Dependence (RD; maintenance of behavior in response to cues of social reward), and 4) Persistence (P; maintenance of behavior despite frustration). These dimensions may be associated with neurotransmitter circuits in the central nervous system (Cloninger, 1986). Indeed, many findings support the biological basis of the model (Cloninger, 2000). This model also

Abbreviations: MDD, major depressive disorder; SUD, substance use disorder; AUP, alcohol use problems; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reward Dependence; P, Persistence; SD, Self-Directedness; C, Cooperativeness; ST, Self-Transcendence; BA, behavioral activation therapy; MI, motivational interviewing; MADRS, Montgomery Åsberg Depression Rating Scale; TCI-R, Temperament and Character Inventory

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comprises character dimensions, which are moderately heritable, mature in adulthood, and influence personal and societal effectiveness on three levels: 1) intrapersonal (Self-Directedness, SD), 2) interpersonal (Cooperativeness, C) and 3) transpersonal (Self-Transcendence, ST) (Cloninger et al., 1993; Cloninger, 2000).

These dimensional temperament and character profiles can be assessed using the Temperament and Character Inventory (TCI-R) (Cloninger, 2000). Several studies have suggested the presence of differences between patients with psychiatric disorders and healthy individuals and although temperament is considered relatively stable throughout human lifespan, also state-dependent alterations are present in depression possibly because of biological changes (Kampman and Poutanen, 2011). Studies comparing patients with MDD and the general population have shown higher HA scores in patients, and HA has also been shown to be both state- and trait-dependent in MDD (Kampman and Poutanen, 2011; Farmer et al., 2003; Richter et al., 2003). Patients with MDD tend to score lower on SD and C, and SD scores are inversely correlated with depressive symptoms (Bensaeed et al., 2014; Hur and Kim, 2009; Nery et al., 2009). In MDD patients, low SD is associated with childhood trauma and recurrence of depressive episodes (Asano et al., 2015; Perna et al., 2014).

High NS scores are associated with substance use problems, predict the development of SUD in high risk groups (Sher et al., 2000), and are related to alcohol relapses, anhedonia and craving in detoxification in substance dependence (Evren et al., 2012; Martinotti et al., 2008; Zilberman et al., 2003). Additionally, high HA scores are associated with alcohol dependence and craving in substance dependent patients (De Los Cobos et al., 2011; Sher et al., 2000). Conversely, SD scores tend to be lower in polysubstance users, and low SD has been associated with DSM-IV cluster B personality disorders in SUD patients (Ball et al., 1997; Yoon et al., 2007).

In MDD patients with a lifetime alcohol dependency diagnosis compared with MDD patients without alcohol dependency, NS was found to be higher whilst P and C are lower (Rae et al., 2002). Another study of exclusively detoxified male alcohol dependent patients found severity of depression and anxiety were predicted by high HA and ST scores, and low P, SD, and C scores (Evren et al., 2009). Patients with dual diagnosis (substance use disorder and severe mental illness) have higher NS and HA and lower RD, SD and C when compared to population norms, and different personality traits vary according to the mental illness (MDD, bipolar disorder or schizophrenia) (Marquez-Arrico et al., 2016; Marquez-Arrico and Adan, 2016). One study has addressed differences in personality between male patients with dual diagnosis and severe mental illness and patients with dual diagnosis seem to have higher NS and lower SD (Fernandez-Mondragon and Adan, 2015).

Studies regarding differences in temperament and character dimensions between depressed patients with comorbid substance use and depressed patients without the comorbidity are limited (Rae et al., 2002) and to our knowledge only one study has addressed this earlier (Fernandez-Mondragon and Adan, 2015). In this study, we explore differences in TCI-R scores at baseline and after 6 weeks of treatment between these two groups with a more significant number of patients. We hypothesized that depressed patients with alcohol use problems (AUP) would have different temperament and character profiles compared with depressed patients without AUP. Human personality seems to be more dynamic in nature than has been earlier thought and recent research has been focused also on the changes in personality and their association with depression outcome (Roberts and DelVecchio, 2000; Klein et al., 2011; Corruble et al., 2002). We aimed to use changes in TCI-R dimensions to predict antidepressive treatment outcome during the first 6 weeks of treatment. SUD comorbidity affects the course of depression and we hypothesized that the different changes in temperament and character between the two studied patient groups would associate with antidepressive treatment outcome.

2. Methods

2.1. Participants

Between 2009 and 2013, we recruited 242 patients from five outpatient clinics and one inpatient unit in the Seinäjoki Hospital District in Finland (population 200,000). The patients were referred to secondary care psychiatric services (specialized care provided by district hospitals) because of depressive symptoms, anxiety, self-destructiveness, insomnia or alcohol-related problems. For inclusion, patients had to have a Beck Depression Inventory (BDI, Version 1A) score of at least 17 (Beck et al., 1996). At screening performed by a clinician patients with a likely or verified psychotic disorder (ICD-10 F2* diagnosis) or organic brain disease were excluded. Patients were aged 17–64 years (mean 38.6 years, SD $\pm$ 12.2). Further sociodemographic data are presented in Table 1a. The study was approved by the local Human Subjects Review Committee and subjects gave informed written consent.

Table 1a
Sociodemographic data of the patient sample.

	Men		Women		AUP		non-AUP		Total	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	88	40.7	128	59.3	89	41.2	127	58.8	216	100
Marital status[a]										
Single	33	37.5	37	28.9	37	41.6	33	26.0	70	32.4
Married or cohabiting	37	42.0	67	52.3	33	37.1	71	55.9	104	48.1
Divorced	18	20.5	21	16.4	18	20.2	21	16.5	39	18.1
Widowed	0	0	2	1.6	0	0	2	1.6	2	0.9
Education[b]										
Primary school	4	4.5	2	1.6	2	2.2	4	3.1	6	2.8
Elementary school	26	29.5	27	21.1	28	31.5	25	19.7	53	24.5
Institute graduate	9	10.2	22	17.2	11	12.4	20	15.7	31	14.4
Vocational school	31	35.2	51	39.8	34	38.2	48	37.8	82	38.0
Graduate student	10	11.4	7	5.5	5	5.6	12	9.4	17	7.9
Polytechnic or university	8	9.1	18	14.1	8	9.0	18	14.2	26	12.0
Work status before sick leave[c]										
Employed	37	42.0	65	50.8	38	42.7	64	50.4	102	47.2
Unemployed	40	45.5	28	21.9	37	41.6	31	24.4	68	31.5
Housewife/husband	0	0	8	6.3	0	0	8	6.3	8	3.7
Pensioner	4	4.5	10	7.8	3	3.4	11	8.7	14	6.5
Student	6	6.8	15	11.7	9	10.1	12	9.4	21	9.7
Self reported history of depression episode[d]	59	67.0	83	64.8	65	73.0	77	60.6	142	65.7
First degree family history of depression[e]	31	35.2	52	40.6	32	36.0	51	40.2	83	38.4
First degree family history of bipolar disorder[f]	3	3.4	10	7.8	4	4.5	9	7.1	13	6.0

Abbreviations: AUP=alcohol use problems.

[a] $\chi^2=9.59$, $p=0.02$ between AUP and non-AUP.
[b] $\chi^2=5.68$, $p=0.3$ between AUP and non-AUP.
[c] $\chi^2=13.47$, $p=0.009$ between AUP and non-AUP.
[d] $\chi^2=3.50$, $p=0.06$ between AUP and non-AUP.
[e] $\chi^2=0.32$, $p=0.6$ between AUP and non-AUP.
[f] $\chi^2=0.59$, $p=0.4$ between AUP and non-AUP.

2.2. Procedures

After screening 26 patients dropped out and 216 patients were analyzed. Demographic and clinical assessments were conducted at baseline during the first visit at secondary care unit (socio-demographic data; Alcohol Use Disorders Identification Test (AUDIT) (Bohn et al., 1995); Montgomery Åsberg depression rating scale (MADRS) (Montgomery and Asberg, 1979); Temperament and Character Inventory (TCI-R) (Cloninger, 2000); and The Mini International Neuropsychiatric Interview 5.0 (MINI) (Sheehan et al., 1998). The MADRS and TCI-R were administered again at 6 weeks during the second visit at secondary care unit. The patients were diagnosed according to DSM-IV criteria with MINI that was administered to 204 patients (data missing in 12 cases) by a psychiatrist or a trained research nurse. We defined the main diagnosis for the patients according to clinical standards and considered depressive disorders as primary, anxiety disorders as secondary and other diagnoses as tertiary. One hundred and eighty-one patients (88.7%) had MDD, 8 (3.9%) had dysthymic disorder, 11 (5.4%) had an anxiety disorder, 3 (1.5%) had self-destructiveness, and one (0.5%) alcohol use disorder as a main diagnosis. Sixty-seven percent of patients with mood disorder as a primary diagnosis had comorbid anxiety disorders. In the total sample, 65.7% of the patients reported having recurrent episodes of MDD.

At recruitment, patients completed the AUDIT questionnaire. Patients were divided into two groups according to AUDIT scores: patients with no alcohol use problems (non-AUP) had scores < 11 and patients with alcohol use problems (AUP) had scores ≥ 11. This cut-off point was chosen because in Finnish clinical practice it indicates significantly increased risk of harm due to alcohol (Babor et al., 2001). After dropout these criteria produced 127 non-AUP patients (mean age 38.5 years, SD $\pm$ 12.8) and 89 AUP patients (mean age 38.7 years, SD $\pm$ 11.4). The MINI was administered to 82 AUP patients (data missing in 7 cases) and 61 (74.4%) of these patients filled the DSM-IV criteria for current alcohol use disorder (AUD). Eight (9.8%) of the patients with AUD filled the criteria for some other current SUD and 16 (19.5%) reported use of some other substance at least once during prior year.

The AUP group had a greater proportion of male patients (AUP 64.0% vs. non-AUP 24.4%, $\chi^2=34.05$, $p<0.001$; odds ratio (OR)= 5.5, 95% confidence intervals (CI)=3.0–10.0). Additional baseline data are presented in Table 1b. All recruited patients were treated in secondary care psychiatric services according to a specific treatment intervention. All patients received behavioral activation therapy (BA) (Kanter et al., 2010), whilst AUP patients also received motivational interviewing (MI) (Miller and Rose, 2009) prior to this. The treatment intervention procedure and related educational program have been described in more detail elsewhere (see ClinicalTrials.gov Identifier NCT02520271 (Ostrobothnia Depression Study (ODS), 2016) and (Lindholm et al., 2015)).

On entering the study, patients' medication was evaluated by a psychiatrist. Antidepressant medication was prescribed to 184 patients (85%) with mean fluoxetine equivalent daily doses of 32.5 mg (SD $\pm$ 18.1). Of these, 80% had either a SSRI or SNRI as a primary antidepressant. Adherence to antidepressants was assessed using a paper and pencil diary during the first 6 weeks. The form was returned at 6 weeks by 99 of the 149 patients (66.4%) who had been prescribed antidepressant medication and hadn't dropped out from the study. Ninety of these (90.9%) had used 80% or more of the medication prescribed. Sixty patients (28%) were prescribed antipsychotic medication with daily chlorpromazine equivalent doses of 118.3 mg (SD $\pm$ 133.5, median=77.1, IQR=91.6). Prescribed antipsychotics included quetiapine in 33 (55%) and other atypical antipsychotics in 7 (12%). Nine patients were treated with a dosage equal to or higher than 200 mg of chlorpromazine per day. Antipsychotic medications were more common in the AUP than the non-AUP group (40.4% vs. 18.9%, $\chi^2=12.12$, $p=0.001$, OR=2.915).

At 6 weeks, 39 patients (26.9%) dropped out of the study. The dropout rate was greater in AUP than non-AUP patients (29% vs. 10%, $\chi^2=12.74$, $p<0.001$), but there were no differences between genders. Dropouts and study completers had similar scores on the MADRS and TCI. However, AUDIT scores were higher in the dropout group than in the total sample (16.85 ± 10.57 vs. 9.13 ± 0.69, $p<0.001$). Corresponding analyses revealed similar results in male and female patients separately.

Table 1b
Baseline scores of BDI and AUDIT between groups.

	Men	Women	AUP	non-AUP	Total
Baseline BDI mean ($\pm$ SD)	28.2 (6.70)	27.1 (7.22)	27.7 (6.88)	27.5 (7.14)	27.6 (7.02)
Baseline AUDIT mean ($\pm$ SD)	15.0 (10.53)	8.1 (8.17)	20.8 (7.03)	3.9 (3.14)	10.9 (9.79)

Abbreviations: BDI=Beck Depression Inventory; AUDIT=alcohol use disorder identification test; AUP=alcohol use problems.

2.3. Statistical methods

Crohnbach's α was calculated to assess the reliability of each TCI-R dimension. We used independent samples *t*-tests to analyze differences between continuous variables (TCI, MADRS, and AUDIT scores) in AUP and non-AUP, between genders, and in the dropout analyses. We analyzed TCI dimension and MADRS changes from baseline to 6 weeks using paired samples *t*-tests. Differences between grouping variables were calculated with χ^2-statistics.

Potential explanatory variables for univariate analysis were explored with Pearson correlation coefficients. First, we built univariate general linear models (GLMs) to predict each TCI dimension at baseline and at 6 weeks with age, and either gender or AUP as explanatory variables. Second, we built a model which included all three variables together with baseline MADRS as explanatory variables. Third, we built GLMs to explain MADRS score change from baseline to 6 weeks (ΔMADRS) with either 1) temperament dimension changes (NS, HA, RD, P) or 2) character dimension changes (SD, C, ST) used as explanatory variables, and age, gender, and AUP in all models. Effect sizes for complete models and individual variables are reported as partial eta square (ηp^2). All analyses were performed with SPSS for Mac or SPSS for Windows software (version 21.0, IBM Inc. Armonk, New York, USA).

3. Results

The Crohnbach's α values for each TCI-R dimension at baseline were: NS 0.85, HA 0.88, RD 0.89, P 0.92, SD 0.86, C 0.85, ST 0.85. Table 2 presents scores for each TCI-R dimension and for the MADRS at baseline and 6 weeks. AUP had higher NS and lower P, SD and C scores at baseline compared to non-AUP. The mean differences between non-AUP and AUP at baseline were: NS= −7.64 (SD $\pm$ 2.30), p=0.001; P=6.54 (2.80), p=0.021; SD=8.08 (2.49), p=0.001; and C=8.41 (2.55), p=0.001. At six weeks AUP had higher NS and lower SD compared to non-AUP. The mean differences between non-AUP and AUP at six weeks were: NS= −6.40 (SD $\pm$ 2.59), p=0.014; SD=11.00 (2.59), p < 0.001. Proportion and significance of changes in each measure and differences between groups are also presented in Table 2.

Results of the GLMs for each TCI-R dimension at baseline and

Table 2
The temperament dimension and MADRS score comparison between groups at baseline and 6 weeks and their changes.

Temperament dimensions	Men			Women			non-AUP patients			AUP patients			All patients		
	Baseline ($n=88$)	6 weeks ($n=70$)	Change; p^*	Baseline ($n=128$)	6 weeks ($n=107$)	Change; p^*	Baseline ($n=127$)	6 weeks ($n=114$)	Change; p^*	Baseline ($n=89$)	6 weeks ($n=63$)	Change; p^*	Baseline ($n=216$)	6 weeks ($n=177$)	Change; p^*
NS (±SD)	104.35 (17.57)[a]	103.31 (17.92)[b]	ns	97.34 (16.09)[a]	97.36 (15.50)[b]	ns	97.05 (17.41)[c]	97.44 (16.95)[d]	ns	104.69 (15.47)[c]	103.84 (15.53)[d]	ns	100.19 (17.02)	99.72 (16.70)	ns
HA (±SD)	115.15 (18.26)	111.46 (16.90)	3.46; 0.010	114.59 (19.85)	114.72 (20.07)	ns	113.71 (19.49)	112.44 (19.27)	ns	116.40 (18.72)	115.22 (18.22)	ns	114.82 (19.18)	113.43 (18.90)	ns
RD (±SD)	93.80 (16.39)[e]	94.74 (17.15)[f]	ns	103.34 (16.31)[e]	103.52 (17.06)[f]	ns	100.69 (17.31)	100.97 (17.30)	ns	97.67 (16.40)	98.38 (18.11)	ns	99.45 (16.97)	100.05 (17.58)	ns
P (±SD)	98.58 (20.65)	99.33 (20.76)	ns	101.97 (20.35)	99.98 (22.09)	−2.15; 0.049	103.28 (20.78)[g]	102.02 (21.84)	ns	96.74 (19.54)[g]	95.57 (20.44)	ns	100.59 (20.49)	99.72 (21.52)	ns
SD (±SD)	117.86 (17.04)[h]	120.54 (16.35)[i]	ns	125.35 (18.78)[h]	128.50 (17.23)[i]	2.30; 0.047	125.63 (18.94)[j]	129.27 (16.14)[k]	3.54; 0.002	117.55 (16.63)[j]	118.27 (17.16)[k]	ns	122.30 (18.42)	125.36 (17.29)	2.29; 0.015
C (±SD)	123.97 (19.26)[l]	125.10 (18.17)[m]	ns	136.12 (16.94)[l]	136.33 (16.59)[m]	ns	134.63 (17.91)[n]	133.64 (17.57)	ns	126.22 (19.16)[n]	128.71 (18.57)	ns	131.17 (18.85)	131.89 (18.04)	ns
ST (±SD)	65.91 (13.64)	66.03 (14.44)	ns	67.12 (14.21)	64.21 (16.25)	−2.71; 0.004	67.47 (14.67)	65.71 (16.13)	−2.39; 0.005	65.42 (12.88)	63.52 (14.43)	ns	66.63 (13.97)	64.93 (15.54)	−1.71; 0.014
MADRS (±SD, *n*)	24.72 (6.22, $n=88$)[o]	18.76 (7.81, $n=74$)[p]	6.51; <0.001	22.01 (6.22, $n=125$)[o]	15.85 (7.97, $n=105$)[p]	6.28; <0.001	22.68 (6.21, $n=126$)	17.00 (7.98, $n=115$)	5.90; <0.001	23.77 (6.53, $n=87$)	17.14 (8.13, $n=64$)	7.22; <0.001	23.13 (6.35, $n=213$)	17.05 (8.01, $n=179$)	6.38; <0.001

Abbreviations: AUP=alcohol use problems; NS=Novelty Seeking; HA=Harm Avoidance; RD=Reward dependence; P=Persistence; SD=Self-Directedness; C=Cooperativeness; ST=Self-transcendence; ns=non-significant; MADRS=Montgomery-Åsberg Depression Rating Scale.

[a] Mean differences at baseline between men and women (±SD): −7.02 (2.31), $p=0.003$.
[b] Mean differences at 6 weeks between men and women (±SD): −5.95 (2.54), $p=0.020$.
[c] Mean differences at baseline between non-AUP and AUP (±SD): −7.64 (2.30), $p=0.001$.
[d] Mean differences at 6 weeks between non-AUP and AUP (±SD): −6.40 (2.59), $p=0.014$.
[e] Mean differences at baseline between men and women (±SD): 9.54 (2.26), $p<0.001$.
[f] Mean differences at 6 weeks between men and women (±SD): 8.78 (2.63), $p=0.001$.
[g] Mean differences at baseline between non-AUP and AUP (±SD): 6.54 (2.80), $p=0.021$.
[h] Mean differences at baseline between men and women (±SD): 7.49 (2.51), $p=0.003$.
[i] Mean differences at 6 weeks between men and women (±SD): 7.96 (2.60), $p=0.003$.
[j] Mean differences at baseline between non-AUP and AUP (±SD): 8.08 (2.49), $p=0.001$.
[k] Mean differences at 6 weeks between non-AUP and AUP (±SD): 11.00 (2.59), $p<0.001$.
[l] Mean differences at baseline between men and women (±SD): 12.15 (2.48), $p<0.001$.
[m] Mean differences at 6 weeks between men and women (±SD): 11.23 (2.65), $p<0.001$.
[n] Mean differences at baseline between non-AUP and AUP (±SD): 8.41 (2.55), $p=0.001$.
[o] Mean differences at baseline between men and women (±SD): −2.71 (0.87), $p=0.002$.
[p] Mean differences at 6 weeks between men and women (±SD): −2.91 (1.20), $p=0.016$.
[*] Change from baseline to 6 weeks with paired samples *t*-test.

Table 3a
GLM results of two models with age and either gender or AUP as explaining variables with explanatory proportions for each individual explanatory variable demonstrating their contribution to temperament dimension scores at baseline and at 6 weeks.

Target variable	Complete model with age and gender as explaining variables			Age		Gender		Complete model with age and AUP as explaining variables			Age		AUP	
	ηp^{2b}	p	power	ηp^{2a}	p	ηp^{2a}	p	ηp^{2b}	p	power	ηp^{2a}	p	ηp^{2a}	p
NS baseline	**0.139**	**< 0.001**	**1.000**	**0.102**	**< 0.001**	**0.057**	**< 0.001**	**0.137**	**< 0.001**	**1.000**	**0.092**	**< 0.001**	**0.054**	**0.001**
NS 6 weeks	**0.109**	**< 0.001**	**0.988**	**0.081**	**< 0.001**	**0.039**	**0.008**	**0.109**	**< 0.001**	**0.988**	**0.077**	**< 0.001**	**0.039**	**0.008**
HA baseline	*0.001*	*0.854*	*0.074*	*0.001*	*0.602*	*< 0.001*	*0.804*	*0.006*	*0.526*	*0.157*	*0.001*	*0.611*	*0.005*	*0.310*
HA 6 weeks	*0.008*	*0.517*	*0.160*	*< 0.001*	*0.797*	*0.007*	*0.258*	*0.005*	*0.638*	*0.123*	*< 0.001*	*0.868*	*0.005*	*0.353*
RD baseline	**0.084**	**< 0.001**	**0.982**	*0.008*	*0.180*	**0.080**	**< 0.001**	*0.012*	*0.274*	*0.280*	*0.004*	*0.332*	*0.008*	*0.197*
RD 6 weeks	**0.068**	**0.002**	**0.895**	*0.008*	*0.225*	**0.063**	**0.001**	*0.011*	*0.389*	*0.213*	*0.006*	*0.315*	*0.005*	*0.336*
P baseline	**0.033**	**0.027**	**0.672**	**0.027**	**0.016**	*0.009*	*0.163*	**0.050**	**0.004**	**0.851**	**0.025**	**0.019**	**0.026**	**0.019**
P 6 weeks	*0.005*	*0.629*	*0.125*	*0.005*	*0.347*	*< 0.001*	*0.800*	*0.026*	*0.100*	*0.469*	*0.006*	*0.324*	*0.021*	*0.053*
SD baseline	**0.117**	**< 0.001**	**0.998**	**0.080**	**< 0.001**	**0.053**	**0.001**	**0.115**	**< 0.001**	**0.998**	**0.072**	**< 0.001**	**0.051**	**0.001**
SD 6 weeks	**0.112**	**< 0.001**	**0.991**	**0.064**	**0.001**	**0.061**	**0.001**	**0.152**	**< 0.001**	**0.999**	**0.064**	**0.001**	**0.103**	**< 0.001**
C baseline	**0.153**	**< 0.001**	**1.000**	**0.058**	**< 0.001**	**0.117**	**< 0.001**	**0.090**	**< 0.001**	**0.988**	**0.044**	**0.002**	**0.051**	**0.001**
C 6 weeks	**0.144**	**< 0.001**	**0.999**	**0.056**	**0.002**	**0.106**	**< 0.001**	**0.061**	**0.004**	**0.856**	**0.045**	**0.005**	*0.019*	*0.065*
ST baseline	0.021	0.105	0.459	**0.019**	**0.043**	*0.003*	*0.431*	*0.023*	*0.080*	*0.507*	**0.018**	**0.048**	*0.005*	*0.280*
ST 6 weeks	**0.039**	**0.031**	**0.655**	**0.036**	**0.012**	*0.002*	*0.539*	**0.042**	**0.023**	**0.692**	**0.038**	**0.010**	*0.005*	*0.330*

AUP = alcohol use problems; MADRS = Montgomery-Åsberg Depression Rating Scale; NS = Novelty Seeking, HA = Harm Avoidance, RD = Reward Dependence, P = Persistence, SD = Self-Directedness, C = Cooperativeness, ST = Self-Transcendence.
Non-significant results are in italics and significant results are in bold.

[a] Explanatory proportion of the single factor or covariate for the target variable.
[b] Explanatory proportion of the complete model for the target variable.

Table 3b
GLM results with explanatory proportions for each individual explanatory variable (age, gender, AUP, and MADRS baseline scores) demonstrating their contribution to temperament dimension scores at baseline and at 6 weeks.

Target variable	Complete model			Age		Gender		AUP		MADRS baseline scores	
	ηp^{2a}	p	power	ηp^{2b}	p	ηp^{2b}	p	ηp^{2b}	p	ηp^{2b}	p
NS baseline	**0.157**	**< 0.001**	**1.000**	**0.097**	**< 0.001**	**0.026**	**0.018**	**0.023**	**0.027**	*0.001*	*0.726*
NS 6 weeks	**0.124**	**< 0.001**	**0.984**	**0.082**	**< 0.001**	*0.015*	*0.105*	*0.017*	*0.089*	*< 0.001*	*0.869*
HA baseline	*0.029*	*0.185*	*0.479*	*0.004*	*0.355*	*0.001*	*0.605*	*0.006*	*0.270*	**0.021**	**0.036**
HA 6 weeks	*0.040*	*0.136*	*0.533*	*< 0.001*	*0.960*	**0.024**	**0.043**	*0.015*	*0.113*	*0.018*	*0.078*
RD baseline	**0.132**	**< 0.001**	**0.998**	*0.011*	*0.122*	**0.051**	**0.001**	*0.001*	*0.647*	**0.057**	**< 0.001**
RD 6 weeks	**0.111**	**< 0.001**	**0.970**	*0.009*	*0.214*	**0.033**	**0.018**	*0.002*	*0.570*	**0.053**	**0.002**
P baseline	**0.050**	**0.031**	**0.746**	**0.025**	**0.022**	*0.001*	*0.590*	*0.017*	*0.057*	*< 0.001*	*0.852*
P 6 weeks	*0.031*	*0.244*	*0.423*	*0.006*	*0.319*	*0.003*	*0.442*	**0.023**	**0.047**	*0.003*	*0.487*
SD baseline	**0.180**	**< 0.001**	**1.000**	**0.103**	**< 0.001**	*0.014*	*0.083*	**0.028**	**0.016**	**0.036**	**0.006**
SD 6 weeks	**0.200**	**< 0.001**	**1.000**	**0.083**	**< 0.001**	*0.008*	*0.249*	**0.066**	**0.001**	**0.028**	**0.028**
C baseline	**0.176**	**< 0.001**	**1.000**	**0.062**	**< 0.001**	**0.061**	**< 0.001**	*0.011*	*0.129*	**0.024**	**0.026**
C 6 weeks	**0.157**	**< 0.001**	**0.998**	**0.059**	**0.001**	**0.066**	**0.001**	*< 0.001*	*0.987*	*0.021*	*0.057*
ST baseline	*0.026*	*0.248*	*0.421*	*0.017*	*0.061*	*0.002*	*0.541*	*0.002*	*0.483*	*0.002*	*0.479*
ST 6 weeks	**0.063**	**0.025**	**0.770**	**0.031**	**0.020**	*0.001*	*0.621*	*0.008*	*0.235*	**0.020**	**0.062**

AUP = alcohol use problems; MADRS = Montgomery-Åsberg Depression Rating Scale.
Non-significant results are in italics and significant results are in bold.

[a] Explanatory proportion of the complete model for the target variable.
[b] Explanatory proportion of the single factor or covariate for the target variable.

6 weeks are presented in Tables 3a and 3b. The models reported in Table 3a included age and either gender or AUP as explanatory variables, and the models presented in Table 3b included age, gender, baseline MADRS score, and patient group (AUP and non-AUP) as explanatory variables for each TCI dimension at baseline and at 6 weeks.

We also applied GLM analyses to MADRS score changes from baseline to 6 weeks (ΔMADRS) as described in Section 2. The temperament model explained 12.2% ($p=0.003$) of the ΔMADRS. In this model, RD change was the only significant explanatory variable, explaining 4.2% ($p=0.009$) of the change. The character model explained 13.7% ($p=0.001$) of the ΔMADRS. In this model, SD change explained 7.2% ($p=0.001$) and ST change explained 3.7% ($p=0.015$) of the ΔMADRS, whilst the other explanatory variables did not contribute significantly to the model.

The above model was also applied to ΔMADRS in the non-AUP and AUP groups separately. The temperament model was non-significant in explaining ΔMADRS in non-AUP patients ($p=0.141$). However, in AUP patients the model explained 28.3% ($p=0.006$) of the ΔMADRS. In this model, RD change explained 14.1% ($p=0.005$) and age explained 11.6% ($p=0.012$) of the ΔMADRS. The character model explained 14.3% ($p=0.007$) of the ΔMADRS in non-AUP patients. In this model, SD change explained 8.0% ($p=0.003$) and ST change explained 5.1% ($p=0.021$) of the ΔMADRS. The character model for the ΔMADRS in AUP patients explained 19.0% ($p=0.043$) of the change. Age explained 9.7% ($p=0.021$) of the ΔMADRS, whilst all character dimension changes did not contribute significantly to the model.

The Pearson correlation coefficient between RD change and ΔMADRS was non-significant ($r=-0.185$, $p=0.054$, $n=109$) in non-AUP patients and significant ($r=-0.377$, $p=0.003$, $n=59$) in AUP patients. There was a significant correlation between SD change and ΔMADRS in non-AUP ($r=-0.301$, $p=0.001$), but non-significant in AUP patients ($r=-0.249$, $p=0.058$). The correlation

between ST change and ΔMADRS was significant in non-AUP patients ($r=0.205$, $p=0.032$), but non-significant in AUP patients ($r=-0.119$, $p=0.368$).

At baseline, correlation coefficients between age and SD, C, and ST were $r=0.260$ ($p<0.001$), $r=0.203$ ($p=0.003$), and $r=0.134$ ($p=0.049$), respectively. At 6 weeks, correlation coefficients between age and SD, C, and ST were $r=0.233$ ($p=0.002$), $r=0.206$ ($p=0.006$), and $r=0.193$ ($p=0.010$), respectively.

4. Discussion

All TCI-R dimensions showed high internal consistency. Our GLMs to predict TCI-R scores showed the association of alcohol use problems with high NS, and low P and SD compared to patients without this comorbidity. Our GLMs to investigate antidepressive treatment response (ΔMADRS) showed an association between RD change and ΔMADRS specifically in the AUP group, highlighting the different psychobiological context of this patient group.

In this study, the temperament profiles of non-AUP patients were similar to previous reports of patients with MDD (Jylhä et al., 2011; Perna et al., 2014). The baseline temperament profiles in our AUP group had significantly higher NS and significantly lower P, SD, and C compared with non-AUP patients, corresponding to the temperament profiles of depressed patients with history of alcohol dependence (Rae et al., 2002). Clinically, this could mean that depressed patients with alcohol use problems are more enthusiastic to try new treatments, but they may show worse treatment adherence because of a lack of self-control, cooperation, and persistence.

High NS is a trait-like characteristic, increasing the risk for SUDs and as such, it tends to be higher in patients with SUD (Sher et al., 2000). Accordingly, the AUP group in this study exhibited higher NS scores compared with non-AUP. Our explanatory model incorporating age, gender, baseline MADRS scores, and patient group accounted for one sixth of the variance in baseline NS scores. Indeed, AUP was a significant explanatory variable for baseline NS scores and there was a trend to significance for 6-week NS scores. Severity of depression did not seem to affect NS scores. Our findings support the role of NS as a trait-like characteristic increasing risk for SUDs, regardless of depressive symptomatology. This emphasizes the importance of recognizing depressed patients showing extravagant lifestyle or thrill seeking as being in a risk of developing a SUD and fit the treatment strategy accordingly.

As expected, HA scores in male patients decreased significantly during the 6-week follow up. There was no significant change in female patients or the whole sample. This is inconsistent with wide evidence regarding the state effect of depression on HA (Kampman and Poutanen, 2011). However, there seems to be a depression spectrum disorder associated with family history of SUDs, recurrent episodes of MDD, higher psychiatric comorbidity, and female gender (Davis et al., 2007; Winokur and Coryell, 1992). Given the more lenient exclusion criteria our sample likely consisted more female patients with recurrent depression and SUD or other psychiatric disorder comorbidities compared to previous studies of temperament in MDD patients. Not finding significant change in female patients HA in our study means that in diverse clinically depressed female patients decrease in harm-avoidant behavior is not associated with depression alleviation. This can lead to high recurrence of depression in these patients because high HA is a trait marker predisposing to depressive episodes (Kampman and Poutanen, 2011). The alleviation of depression in these patients might also be more associated with the reward mechanisms in brain, possibly leading to reward-seeking behavior such as substance use.

The associations of different temperament and character traits with depression recovery have been widely studied, but the associations of different changes in these traits with the antidepressive treatment outcome is a less studied subject although some significant findings have been reported (Corruble et al., 2002). We particularly wanted to investigate possible interactive effects of AUP with temperament and character change on response as a novel focus. Therefore, we built a GLM for ΔMADRS, incorporating age, gender, AUP, and temperament dimension changes as explanatory variables. In this model, RD dimension score change was the only significant variable in explaining ΔMADRS. This was unexpected because there is no evidence for RDs state dependence in depression. In a post-hoc analysis, with corresponding GLMs applied separately to AUP and non-AUP patients, the model was non-significant in the non-AUP group. However, in the AUP group it explained over one fourth of the variance in ΔMADRS, and the increase in RD contributed independently to the antidepressive treatment response. This could mean that the depressive symptoms in patients with alcohol use problems are more related with loss of energy, appetite loss, vegetative symptoms or subjective dysphoria (Grucza et al., 2003) and could be explained with differences in the function of brain anti-reward mechanisms associated with noradrenergic circuits and the hypothalamic-pituitary-adrenal (HPA) axis, with potential moderation by endogenous oxytocin (Bell et al., 2006; Buisman-Pijlman et al., 2014; Cloninger, 1986; Koob and Le Moal, 2008). There may be more reactive depression state dependent changes in these functions reflected in altered RD scores, which are a marked predictor of antidepressive treatment response in AUP patients. However, these associations are speculative and further studies would be needed for confirming them. Furthermore, these mechanisms may be more important in depressive symptomatology of female AUP patients as discussed above.

Previous evidence suggests that lifetime alcohol dependence in MDD patients is associated with low P and severity of depressive symptoms correlates with low P in alcohol dependent patients (Evren et al., 2009; Rae et al., 2002). In our study, age, gender, baseline MADRS scores, and patient group only explained 5% of the baseline P scores and were all non-significant at 6 weeks. At baseline AUP was trending to significance and at 6 weeks it was the only independently significant variable in explaining Persistence (Table 3b). These results are consistent with earlier studies, suggesting that low P is associated with SUD in depressed patients and that such patients' depressive symptoms may include a more profound loss of energy and appetite (Grucza et al., 2003).

In our sample, AUP patients also had significantly lower SD compared with non-AUP patients and our GLM explained one fifth of the variance in SD. It has been proposed previously that control perception (i.e. locus of control) follows from the brain's capacity for self-regulation, leading to flexible and goal-directed behaviors (Declerck et al., 2006). The locus of control can be regarded as reflecting similar traits that are associated with SD, e.g., self-sufficiency, responsibility, reliability, and goal orientation (Cloninger et al., 1993). It has been suggested that these self-regulatory functions are associated with the functions in dorsolateral and ventral prefrontal cortex, and the anterior cingulate cortex (Declerck et al., 2006). Neuropathological changes associated with excessive alcohol use are partly located in these brain regions (Harris et al., 2008). Disrupted theory of mind in patients with alcohol use disorders could reflect altered brain function, which is also reflected in the finding of lower SD in the AUP group (Bosco et al., 2014; Harris et al., 2008).

There was a highly significant positive change in SD scores in non-AUP patients. Our GLM suggested that this change contributed significantly to ΔMADRS during the follow up. This is

consistent with earlier evidence for the state dependence of SD in depression (Nery et al., 2009; Corruble et al., 2002). Psychosocial treatment in this study was standardized and we used BA as a treatment intervention for all patients in our study because it has proven effective in the treatment of MDD, including comorbid or treatment resistant cases, and in patients with personality disorders (Bottonari et al., 2008; Dimidjian et al., 2006; Dobson, et al., 2008; Moradveisi et al., 2013; Weinstock et al., 2011). BA techniques include activity monitoring, assessment of goals and values, and activity scheduling. These presumably can lead to improvement in traits associated with higher SD: self-sufficiency, responsibility, reliability, and goal orientation (Cloninger et al., 1993; Kanter et al., 2010). However, despite also receiving BA, there was no change in SD scores in AUP patients. This might suggest that these patients, due to lower self-reflecting capacity caused by disrupted brain functions, receive a more limited benefit from psychotherapeutic interventions at the acute stage of treatment (Bosco et al., 2014; Declerck et al., 2006; Harris et al., 2008).

Although C was significantly higher in AUP group, AUP failed to explain C scores in the GLM. Age was associated with C scores and there were also significant correlations between age and character dimension scores, reflective of character maturation during adulthood (Cloninger et al., 1993). Gender contributed the most to variance in C scores, and C is generally higher in women (Yamasue et al., 2008). Therefore, we suggest that unequal gender distributions in AUP and non-AUP groups explain the difference in C scores between these groups. As mentioned, all patients received BA. We hypothesized that BA is able to enhance a patient's self-regulatory and social functions, which will be reflected in the character traits and that trait changes result in alleviation of depressive symptoms. The GLM incorporating character dimension changes, age, gender, and AUP as explanatory variables aimed to explain the role of character traits in the alleviation of depression. According to this model, changes in C were non-significant in explaining decreases in depressive symptoms at 6 weeks, unlike the other two character dimensions SD and ST. This means that alleviation of depressive symptoms at the acute stage are more associated with the enhancement in patient's self-view and decrease in transpersonal identification than with their ability to cooperate.

The role of the ST in depressive symptomatology is so far unclear and there are inconsistencies in findings from different demographic areas (Farmer et al., 2003). There seems to be weak correlation between ST and depressive states, but some studies have shown non-significant or opposite results (Farmer and Seeley, 2009; Nery et al., 2009; Richter et al., 2003; Spittlehouse et al., 2010). In our sample, there was a significant decrease in ST scores in non-AUP patients during the 6-week follow up. Furthermore, changes in MADRS scores were partly explained by changes in ST scores, suggesting an association between severity of depressive symptoms and high ST.

To specifically analyze the effects and possible interactions of age and gender, or age and AUP, separate analyses were performed for each temperament or character dimension. These results resulted in no interactive effects between age and gender or age and AUP. In the model with age and gender as explaining variables gender was significant in both baseline and six-weeks models contrary to the models also including depression severity as an explaining variable. Otherwise the results in these models were in line with the complete model including age, gender, patient group and baseline MADRS scores as explaining variables. This difference in the two models is likely to reflect the difference in gender distributions between AUP and non-AUP groups.

The 'real-life' setting, broad inclusion criteria, and few exclusion criteria posed some challenges and limitations for our study. However, the minimal set of criteria provide results that achieve high clinical relevance and generalizability. The patient sample comprised quite severe cases of depression with marked comorbidity and recurrent MDD episodes, but almost all patients had a diagnosis of MDD. We studied the effects of alcohol use, but some of the patients used also other substances which could have affected the results. Although the use of other substances was infrequent and monitored with MINI and a question of use of other substances during prior year, the data on the type of substances used was not collected. The prescribed medications were diverse, but the majority of patients were prescribed an SSRI or SNRI. The anticipated efficacy of the prescribed medication was evaluated by a psychiatrist and adherence to medical treatment was monitored. Six-week follow-up in the study can be considered as a short time period for analyzing response to treatment, although marked decrease in MADRS scores was observed. As the primary aim of the study was to analyze the effect of alcohol use on temperament and character dimensions, no further analyses were performed in relation to the observed changes in personality with a clinical data and response. However, age, gender and depression severity were taken into account as confounding factors in multivariate analysis. We observed expected uneven gender distributions between the non-AUP and AUP groups. This prevented interpretation of temperament profile differences solely through bivariate comparisons, and required the use of multivariate analyses, as well as gender-wise divisions. It is possible that these multiple statistical analyses could lead to type 1 errors as no correction for multiple testing was used. It is however notably, that the bivariate analyses were exploratory in nature and the final interpretation of the results was made according to the multivariate analyses.

Depressed patients with alcohol use problems had lower Self-Directedness and Persistence and higher Novelty Seeking compared with depressed patients without the comorbidity. Clinically, this could explain why depressed patients with alcohol use problems are more enthusiastic to try new treatments, but show worse treatment adherence. Changes in Reward Dependence and lower Self-Directedness in AUP patients could be reflective of different biological mechanisms associated with depressive symptomatology in substance abusive patients. The increase in Self-Directedness and decrease in Self-Transcendence associated with alleviation of depression in non-AUP, but there were no changes in character dimensions in patients with alcohol use problems suggesting that these patients could benefit less from behavioral activation therapy at acute stage of treatment.

Conflicts of interest

Olli Kampman has consulted for Medivir; received speaker´s fees from Janssen-Cilag and received support from Otsuka and Lundbeck to participate in an international congress.

Esa Leinonen has worked as a lecturer or chairman in symposia sponsored by pharmaceutical companies Astra-Zeneca, Eli Lilly, Lundbeck and Servier; served on the national advisory board of Servier and received support from Astra-Zeneca, Lundbeck, Otsuka and Servier to participate in international congresses.

Antti Koivukangas has been invited as a lecturer by pharmaceutical company Orion.

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Temperament and character profiles are associated with depression outcome in psychiatric secondary care patients with harmful drinking

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ABSTRACT

Background: Temperament and character profiles have been associated with depression outcome and alcohol abuse comorbidity in depressed patients. How harmful alcohol use modifies the effects of temperament and character on depression outcome is not well known. Knowledge of these associations could provide a method for enhancing more individualized treatment strategies for these patients.
Methods: We screened 242 depressed patients with at least moderate level of depressive symptoms. The Alcohol Use Disorders Identification Test (AUDIT) was used for identifying patients with marked alcohol use problems (AUP, AUDIT≥11). After 6 weeks of antidepressive treatment 173 patients were assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Temperament and Character Inventory (TCI-R). Outcome of depression (MADRS scores across three follow-up points at 6 weeks, 6 months and 24 months) was predicted with AUP, gender, and AUP x Gender and AUP x Time interactions together with temperament and character dimension scores in a linear mixed effects model.
Results: Poorer outcome of depression (MADRS scores at 6 weeks, 6 months and 24 months) was predicted by AUP × Time interaction ($p = 0.0002$) together with low Reward Dependence ($p = 0.003$). Gender and all other temperament and character traits were non-significant predictors of the depression outcome in the mixed effects model.
Conclusions: Possibly due to the modifying effect of alcohol use problems, high Reward Dependence was associated with better depression treatment outcome at 6 months. Harm Avoidance and Self-Directedness did not predict depression outcome when alcohol use problems were controlled.

1. Introduction

It is well known that comorbidity of major depressive disorder (MDD) with substance use disorders (SUDs) can lead to impaired response to treatment, more chronic disease courses or recurrence of depressive episodes [1,2]. Because recurrent and chronic depression constitute a major burden of disease [1,2], more efficient treatment strategies and means for earlier identification of high-risk patients are needed.

Assessment of individual temperament and character traits could provide a method for enhancing preventive and more individualized treatment strategies for these patients because certain traits and temperaments may predispose individuals to recurrence of depression, and are associated with different courses of depression and with substance use disorder comorbidity and drinking outcomes [3–6]. Individual personality could have pathoplastic effects on recovery from depression; i.e., differences in temperament or character could explain differences in the course of the illness [7]. How harmful alcohol use modifies the effects of temperament and character on depression outcome is not well known.

The Temperament and Character inventory (TCI-R) is a 240-item questionnaire that collects information on human personality in the context of temperament and character. According to Cloninger's psychobiological model, on which the TCI-R was based, temperament is divided into four dimensions: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P). Character is divided into three dimensions: Self-Directedness (SD), Cooperativeness (C) and Self-Transcendence (ST) [8]. These dimensions are thought to

Abbreviations: MDD, major depressive disorder; SUD, substance use disorder; NS, novelty seeking; HA, harm avoidance; RD, reward dependence; P, persistence; SD, self-directedness; C, cooperativeness; ST, self-transcendence; AUP, alcohol use problems; MADRS, Montgomery-Åsberg Depression Rating Scale; TCI-R, Temperament and Character Inventory.

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reflect combinations of different neurocognitive functions (e.g., memory or reward functions), and the biological basis of this model is supported by many findings [9,10].

According to Cloninger's theory, temperament dimensions generally represent a stable part of personality, and only HA has shown clear state-dependent changes during depression [4,5,8]. However, high HA – and more particularly its sub-scores, anticipatory worry (HA1) and fatigability (HA4) – have also manifested as trait-like markers for risk of depression, i.e., index episodes, relapses or recurrent episodes and impaired treatment response [4,5]. High RD could be protective against depression in general population, but no associations have been reported with outcome of depression in clinically depressed patients [4,11–15]. Our earlier study of this patient sample suggested that RD is associated with depression treatment outcome in patients with alcohol use problems as change in RD was strongly associated with acute treatment response (0–6 weeks) to depression when alcohol use was taken into account [16]. High NS is a trait indisputably associated with risk of substance use disorders, more severe symptomatology and poorer outcome in SUD patients, and apparently experienced at a higher level in patients with dual diagnosis (concurrent SUD and mental illness) than in depressed patients [3,6,17–20]. Low P and high HA are associated with more severe alcohol dependence symptomatology [21–23].

Of the character traits, low SD is the trait most clearly predisposing to depression and recurrence of episodes, possibly because individuals with deficiencies in sub-traits such as self-acceptance, responsibility, goal-directedness associated with SD may be more prone to depression due to difficult situations encountered in their daily lives [24,25]. There is less evidence to suggest that low C is associated with the development of depression, whereas findings on the associations between ST and depression in different patient samples have been contradictory [4,15,26,27]. Low SD is also associated with more severe symptomatology and drinking outcomes in SUD patients [6,28,29]. In alcohol dependence character profile with high ST and low SD and C is associated with depression and anxiety [21].

In spite of a large body of knowledge of different associations separately between temperament and character traits and depression or substance use disorders, we found no follow-up studies addressing the associations between depression outcome and temperament, character and alcohol use. We investigated whether temperament and character trait scores (at 6 weeks) together with harmful alcohol use predict outcome of depression in follow-up from 6 weeks to 6 months and to 24 months in a clinically diverse sample of depressed patients. In light of earlier evidence we hypothesize that high HA and low SD and harmful alcohol use together explain poorer depression treatment outcome (measured as MADRS scores) [4,5,25]. As harmful alcohol use had a modifying effect on both temperament and character dimensions during acute illness, we hypothesize that RD together with alcohol use is also associated with outcome of depression in the long-term follow-up (from 6 weeks to 6 and 24 months) [16]. High NS has been associated with more severe SUDs, and therefore we also hypothesized that this temperament trait might modify treatment outcome together with harmful alcohol use in depression [6].

2. Methods

2.1. Participants

In the period 2009–2013, 242 patients were screened for the study in the Finnish region of Southern Ostrobothnia (population 200,000). These patients were referred to psychiatric specialized care units (5 outpatients and 1 inpatient) due to depression, anxiety, self-destructiveness, insomnia or alcohol-related problems. To maximize clinical relevance, lenient inclusion criteria were used. Patients with at least moderate depressive symptomatology (Beck Depression Inventory [BDI] Version 1A, score ≥17; [30]) were included in the study. Patients with organic brain disease or psychotic disorder (ICD-10 F2* diagnosis) were excluded. Their age range was 17–64 years (mean 38.8 years, SD ± 12.2). A more detailed description of the sample is presented in Tables 1a and 1b, and of the study setting elsewhere (see ClinicalTrials.gov Identifier NCT02520271, Ostrobothnia Depression Study [ODS] [43]). The study was approved by the local Human Subjects Review Committee, and patients gave their informed written consent.

2.2. Procedures

Sociodemographic data were collected and clinical assessments conducted at screening (the Alcohol Use Disorders Identification Test (AUDIT) [31] and the BDI). There was some dropout before the baseline assessment using the Mini International Neuropsychiatric Interview 5.0 (MINI; [32]) and the Montgomery-Åsberg Depression Rating Scale (MADRS) [33] and 228 (94%) patients were assessed with MADRS at baseline. According to the MINI administered to 219 patients (data missing in 23 cases), 88.6% of the patients had MDD, 4.1% dysthymic disorder, 5.5% anxiety disorder and 0.4% alcohol use disorder (AUD) as their main diagnosis, and 1.4% of the patients did not meet any of the diagnostic criteria. Twelve percent (12%) of the patients met the criteria for lifetime diagnosis of (hypo)manic episode. Sixty-three percent (63%) of patients with mood disorder as their main diagnosis had comorbid anxiety disorders, corresponding well to comorbidity proportions found in other samples in Finnish psychiatric secondary services [34]. Six patients (3%) with mood disorder as primary diagnosis had comorbid bulimia nervosa. Patients' categorical personality disorder diagnoses were not assessed. In the total sample, 33.6% of the patients reported that this was their first episode of MDD.

At baseline patients attended an appointment with a psychiatrist, where their medication was evaluated and changed if necessary. Antidepressant medication was prescribed to 206 patients (85%) with mean fluoxetine equivalent daily doses of 33.0 mg (SD ± 18.3). Of these, 82% had either an SSRI or SNRI as a primary antidepressant. Adherence to antidepressants was monitored during the first six weeks of the study using a paper and pencil diary (for more information see [16]). All patients received behavioral activation therapy with trained clinical staff. The median number of therapy sessions with patients was 6 (IQR = 3–11) with sessions taking place at 1 to 2-week intervals. The treatment of patients with alcohol use problems (AUP, AUDIT scores ≥11) was enhanced with motivational interviewing (median

Table 1a
Sociodemographic data on the patient sample.

	Men		Women		Total	
	N	%	*N*	%	*N*	%
Total	94	38.8	148	61.2	242	100
Marital status						
Single	34	36.9	39	29.1	73	32.3
Married or cohabiting	39	42.4	71	53.0	110	48.7
Divorced	19	20.7	21	15.7	40	17.7
Widowed	0	0	3	2.2	3	1.3
Education						
Primary school	4	4.3	3	2.2	7	3.1
Comprehensive school	27	29.3	28	20.7	55	24.2
Tertiary education	10	10.9	25	18.5	35	15.4
Vocational school	33	35.9	54	40.0	87	38.3
Upper secondary education	10	10.9	7	5.2	17	7.5
Polytechnic or university	8	8.7	18	13.3	26	11.5
Work status before sick leave						
Employed	39	42.9	67	50.0	106	47.1
Unemployed	41	45.1	30	22.4	71	31.6
Housewife/husband	0	0	10	7.5	10	4.4
Pensioner	5	5.5	11	8.2	16	7.1
Student	6	6.6	16	11.9	22	9.8
Self-reported history of depression episode	62	67.4	90	65.7	152	66.4
First degree family history of depression	33	35.9	56	41.5	89	39.2
First degree family history of bipolar disorder	4	4.3	10	7.4	14	6.2

Table 1b
Baseline scores on BDI and AUDIT by gender.

	Men	Women	Total
Baseline BDI mean (±SD)	28.5 (6.80)	27.5 (7.59)	27.9 (7.30)
Baseline AUDIT mean (±SD)	15.1 (10.59)	7.9 (8.30)	10.7 (9.88)

Abbreviations: BDI = Beck Depression Inventory; AUDIT = Alcohol Use Disorder Identification Test.

number of sessions 4, IQR = 3–6) at the start of the treatment according to a specific treatment intervention procedure (see ClinicalTrials.gov Identifier NCT02520271, Ostrobothnia Depression Study [ODS], 2016 and [35]). The cut-off point for AUDIT was chosen because in Finnish clinical practice it indicates a significantly increased risk of harm due to alcohol [36,37]. In the present study setting the aim was to identify individuals with marked alcohol use problems with high specificity to obtain motivational interview as an add-on psychosocial treatment.

After dropout at 6 weeks, 173 patients completed both the TCI-R and MADRS and were therefore eligible for inclusion in the main analysis of this study. Of these patients 61 (35%) showed marked alcohol use problems (AUP, AUDIT scores ≥11) roughly corresponding to the comorbidity ratio of 2:1 (of substance use disorders in depressed patients) observed in clinical samples where nearly one third of patients with major depressive disorder also have substance use disorders [38]. Of the 61 AUP patients MINI diagnosis had been assessed in 60 cases at baseline, 44 (73%) of which had been diagnosed with lifetime AUD and of the other 112 patients (with AUDIT scores <11) MINI diagnosis had been assessed in 107 cases, only 3 (3%) of which had been diagnosed with lifetime AUD. Seven (16%) patients that had been diagnosed with AUD had also other SUD, and two (2%) patients without AUD were diagnosed with some other SUD. There was no exclusion of patients according to substance use. Alcohol use problems were more common in male patients: (males 69% vs. females 31%, $\chi^2 = 31.5$, $p < 0.001$; odds ratio (OR) = 6.6, 95% confidence intervals (CI) = 3.3–13.2). The follow-up included assessment of patients' MADRS scores again at 6-month and 24-month time-points.

2.3. Statistical methods

Differences in continuous variables (AUDIT and MADRS scores, and TCI-R dimension scores) between dropouts and other patients were calculated with independent samples *t*-tests. Differences in nominal variables between dropouts and other patients and in the prevalence of AUP between genders were calculated with χ^2 statistics.

This study was conducted according to the intention-to-treat protocol and in cases of dropout MADRS scores were imputed in the follow-up according to the last observation carried forward (LOCF) method. This replaced missing values in MADRS follow-up with their last observed values at earlier follow-up time points. This replaced missing MADRS values in 32 (17%) cases at 6-month follow-up and in 93 (49%) cases at 24-month follow-up. Exploratory analysis between LOCF MADRS scores and temperament or character scores was performed with Pearson's correlation coefficients.

A linear mixed effects model was used for the repeated measurement testing in the main analysis of the study. This model predicted LOCF MADRS scores from 6 weeks to 6 months and to 24 months with the scores of the seven temperament and character dimensions (NS, HA, RD, P, SD, C, and ST; at six weeks) used as explaining variables and was adjusted with AUP, gender, and AUP x gender and AUP x time interactions. Individual-specific intercept and slope terms were used in the model. The −2 log likelihood information criteria was used in evaluating model fit and model with unstructured covariance structure was reported. Kenward-Roger adjustment of degrees of freedom was applied for estimates of fixed effects. The main analysis was performed with PROC MIXED, SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and all other analyses were performed with SPSS for Mac (version 24.0, IBM Inc., Armonk, New York, USA).

3. Results

The dropout rate in the study was 65 (27%) at six weeks, 91 (38%) at six months, and 147 (61%) at 24 months, but no gender differences were seen at any assessment point. Of these patients, the clinical treatment had been concluded in co-operation with the patients in 10 (11%) cases during the first 6 months and in 28 (19%) cases before 24 months. The dropout analysis of the raw data revealed similar baseline MADRS scores in dropouts and other patients. Baseline AUDIT scores were higher in dropouts at both rating points (6 months: dropout 14.0 ± 11.2 vs. other patients 8.9 ± 8.6, $p < 0.001$; 24 months: 12.0 ± 10.5 vs. 8.7 ± 8.5, $p = 0.006$ for *t*-test). Dropouts also had lower Self-Directedness at baseline than did other patients in dropout analysis at 6 months: dropout 117.9 ± 18.3 vs. other patients 124.2 ± 18.2, $p = 0.02$ for *t*-test, and had trending but non-significant difference at 24 months ($p = 0.09$). In the LOCF data there were no statistically significant differences between dropouts and other patients' 6-month LOCF MADRS scores in the 6-month dropout analysis ($p = 0.2$ for t-test). Dropouts had higher 24-month LOCF MADRS scores in the 24-month dropout analysis (dropout 12.9 ± 8.9 vs. other patients 8.3 ± 7.6, $p < 0.001$ for t-test).

The main results emerging as predictors of depression treatment outcome (measured as MADRS scores) are presented in Table 2. Poorer outcome of depression was predicted by AUP × Time interaction together with low RD. The model resulted in steeper negative sloping of MADRS scores for non-AUP group when compared to AUP group × Time. This means that alcohol use problems associated with poorer outcome of depression in the follow-up from 6 weeks to 6 months and to 24 months. Low RD was the only temperament or character trait that was associated with depression outcome as a predictor of poorer outcome in the follow-up from 6 weeks to 6 and 24 months.

The distributions (mean ± SD) for LOCF MADRS scores were: 1) 13.6 ± 8.5 at 6 months and 2) 10.6 ± 8.5 at 24 months. The mean ± SD for temperament and character dimensions at six weeks were: NS 99.7 ± 16.7; HA 113.4 ± 18.9; RD 100.1 ± 17.6; P 99.7 ± 21.5; SD 125.4 ± 17.3; C 131.9 ± 18.0; ST 64.9 ± 15.5. The Cronbach's α values for TCI-R dimensions have been reported elsewhere [16]. The MADRS scores, number of responders, remitted patients, and non-responders in follow-up are presented in Table 3.

Pearson's correlation coefficients between RD, HA and SD and LOCF MADRS scores were statistically significant for RD and MADRS scores at 6 months ($r = -0.32$, $p < 0.001$), HA and MADRS scores at 6 months ($r = 0.18$, $p = 0.02$), SD and MADRS scores at 6 months ($r = -0.27$, $p < 0.001$), HA and MADRS scores at 24 months ($r = 0.26$, $p = 0.001$), and SD and MADRS scores at 24 months ($r = -0.32$, $p < 0.001$).

4. Discussion

The main hypotheses in this study were that temperament and character traits together with harmful alcohol use (assessed in the early stages of treatment) explain outcome of depression over a period of two years. The main finding in this study was that poorer outcome of depression was predicted by low Reward Dependence. Alcohol use problems were also associated with poorer outcome of depression in the follow-up from 6 weeks to 6 months and to 24 months.

4.1. Outcome of depression (from 6 weeks to 24 months)

Poorer outcome of depression was predicted by low Reward Dependence in the linear mixed effects model adjusted with AUP, gender, AUP × gender and AUP × time. In contrast to some earlier studies our present and earlier findings suggest that Reward Dependence is associated with depression treatment outcome [4,16,26]. This difference in

Table 2
Predictors of depression outcome (LOCF MADRS scores across the follow-up from 6 weeks to 6 months and to 24 months).[a]

Fixed effects	LOCF MADRS scores			
	Estimate[b]	SE	*t*	*p*
Intercept	**20.07**	**10.04**	**2.00**	**0.049**
NS at 6 weeks	0.04	0.03	1.16	0.25
HA at 6 weeks	0.06	0.04	1.70	0.09
RD at 6 weeks	**−0.11**	**0.04**	**−3.03**	**0.003**
P at 6 weeks	−0.03	0.03	−1.10	0.27
SD at 6 weeks	−0.06	0.04	−1.59	0.11
C at 6 weeks	0.02	0.04	0.56	0.58
ST at 6 weeks	0.05	0.03	1.49	0.14
Male gender	0.24	1.76	0.14	0.23
AUP	3.67	1.64	2.25	0.12
AUP × Male gender	−3.24	2.19	−1.48	0.14
AUP × Time	**−0.10**	**0.05**	**−1.98**	**0.0002**
non-AUP × Time	**−0.33**	**0.06**	**−3.75**	**0.0002**

−2 × log-likelihood = 3530 for the SAS input code and output results.
Abbreviations: LOCF = Last observation carried forward; NS = Novelty Seeking; HA = Harm Avoidance; RD = Reward Dependence; P = Persistence; SD = Self-Directedness; C = Cooperativeness; ST = Self-Transcendence; MADRS = Montgomery-Åsberg Depression Rating Scale; AUP = alcohol use problems.
Significant results are presented in bold face.
[a] Results from the linear mixed effects model with temperament and character dimension scores, gender, AUP, and AUP x Gender and AUP x Time interactions as explanatory variables.
[b] *B* for the temperament and character variables effect on the dependent variable.

results could be explained by differences in patient samples, as patients with SUDs have been excluded in those earlier studies but not in this present one [4,16,26]. Our earlier and present results suggest that low RD predicts poorer outcome of depression particularly in depressed patients with comorbid alcohol use problems. In line with these findings, one study in which patients with prior SUD were not excluded resulted in MDD patients in remission having higher RD than currently depressed patients [24]. More specifically, the presence of SUD together with severe mental illness (SMI, including patients with MDD or schizophrenia) seems to be associated with low RD as dually diagnosed patients have lower RD than do SUD patients, but there is no significant difference in trait RD between patients with SMI or SUD without the comorbidity of the other [3]. The finding of an association between high RD (at 6 weeks) and better outcome of depression together with our earlier finding may be explained by depression state-dependent alterations in brain reward pathway functions in patients comorbid with SUD, and hence confirm a possible association between Reward Dependence and depression treatment outcome when alcohol use problems are taken into account [16,39].

Although high HA and low SD have been associated earlier with risk of recurrences of depressive episodes as well as impaired depression treatment response [4,5,25], surprisingly, in this study these temperament and character traits were not statistically significant in predicting the outcome of depression. One possible explanation for this would be that alcohol use problems in part mediate the association between these personality traits and depression outcome. This argument is justified because earlier findings have shown that AUDs are associated with both: 1) the development of more chronic courses of depressive symptomatology [1,2], and 2) high HA and low SD. More specifically high HA and low SD are both associated with dual diagnosis [3], and high HA also with more severe AUDs [22]. Moreover, it is plausible that lower ability to organized problem solving or greater distress associated with avoidant behavior that are associated with low SD and high HA, respectively, could predispose these individuals to a higher risk of alcohol use problems. Finding the Harm Avoidance and Self-Directedness statistically non-significant in predicting outcome of depression in our analysis with the control of AUP is in line with the argument that the association between high HA and low SD and poorer outcome of depression could be in part mediated by alcohol use problems.

In the main analysis AUP × Time was highly significant predictor of depression outcome and was associated with slower decline of MADRS scores in the follow-up when compared to non-AUP. This finding demonstrates the disruptive effect of alcohol use problems on the outcome of depression and is in line with earlier findings of the detrimental effect of AUDs on the course depression [1,2]. Novelty Seeking, Persistence, Self-Transcendence and Cooperativeness remained non-significant in predicting the outcome of depression when AUPs were taken into account. Although high NS could cause impaired response to antidepressive treatment because it is associated with more severe SUD symptomatology [6,18,20], it seems that high NS is not an important trait in the association with poorer outcome of depression when AUP are controlled. Similarly low Persistence seems to be a marker for more severe or chronic SUD [21,23,40], but it was not a significant marker in predicting depression outcome in this study. The results from different patient samples have been partially contradictory regarding associations between trait ST and depressive symptomatology and the present results suggest that ST alone is not significant in predicting depression outcome nor together with AUP [4,15,26,27]. Although high Cooperativeness could be protective of depression and associated with better drinking outcomes in depressed alcohol-dependent patients [4,6] it was a non-significant predictor of the outcome of depression together with alcohol use problems in this study and this association should be verified in larger samples. As gender has not been associated with severity or recurrence of MDD episodes [2], it was expected that it would likewise not predict depression outcome in this sample of more diverse depressed patients.

Table 3
MADRS scores in raw data, LOCF data, and by patient subgroup and number of responders, patients in remission and non-responders at baseline and follow-up.

	Baseline	6 weeks	6 months	24 months
Raw data MADRS scores (mean ± SD)	23.2 ± 6.7; *n* = 228	16.9 ± 8.0; *n* = 188	13.1 ± 8.7; *n* = 156	8.3 ± 7.6; *n* = 95
Response[a] (n, %)			69, 44%	64, 67%
Remission[b] (n, %)			49, 31%	50, 53%
LOCF data MADRS scores, n = 188			13.6 ± 8.5	10.6 ± 8.5
Response[a] (n, %)			80, 43%	112, 60%
Remission[b] (n, %)			52, 28%	80, 43%
MADRS scores of patient subgroups (raw data scores):				
Non-AUP (mean ± SD)	22.9 ± 6.7 (*n* = 136)	16.7 ± 8.0 (*n* = 123)	12.8 ± 8.7 (*n* = 105)	6.7 ± 6.2 (*n* = 66)
AUP (mean ± SD)	23.7 ± 6.7 (*n* = 92)	17.2 ± 8.1 (*n* = 65)	13.7 ± 8.7 (*n* = 51)	12.0 ± 9.2 (*n* = 29)
Female (mean ± SD)	22.3 ± 6.8 (*n* = 137)	15.7 ± 7.8 (*n* = 112)	11.6 ± 8.2 (*n* = 97)	7.1 ± 6.6 (*n* = 64)
Male (mean ± SD)	24.6 ± 6.3 (*n* = 91)	18.6 ± 8.0 (*n* = 76)	15.6 ± 9.1 (*n* = 59)	10.8 ± 8.9 (*n* = 31)
Proportion of men (n, %)	91, 40%	76, 40%	59, 38%	31, 33%
Proportion of AUP patients (n, %)	92, 40%	65, 35%	51, 33%	29, 31%
Number of patients with increase in symptoms from baseline (n, %)			23, 15%	3, 3%

Abbreviations: AUP = Alcohol use problems; MADRS = Montgomery-Åsberg Depression Rating Scale; LOCF = last observation carried forward.
[a] At least 50% MADRS score decline from baseline.
[b] MADRS scores <8.

4.2. Strengths and limitations

In the mixed effects multivariate model we analyzed the factors predicting the outcome of depression (MADRS scores) across three different time-points (at 6 weeks, 6 months and 24 months). Because depressive episodes are on average of 6 months' duration, the follow-up period up to 6 months is a good marker for responsiveness to antidepressive treatment, whereas follow-up period up to 24 months is likely to reflect considerably more the long-term fluctuation in symptoms, also including relapses and recurrences of depressive episodes [41,42]. It was important to study the outcome across both of these outcomes, because in the majority of cases recovery from depression is not a straightforward process but instead takes a fluctuating course with remissions, relapses, and recurrences of episodes [42]. Moreover, it is possible that traits associated with responsiveness to treatment could in part differ from the traits predisposing to recurrence of episodes and this could be interesting hypothesis to test in future studies in naturalistic samples [4].

As there was marked dropout in this study, especially at 24-month follow-up, data imputation was conducted for the main analysis. The method of last observation carried forward was used even though it could result in more conservative results. It is possible that the LOCF method used in this study did not detect all relapses, but the risk that it would have markedly affected the results in this study was considered low because the naturalistic study setting allowed patients to continue in the study even if they had failed to attend at some earlier point.

According to the theory of pathoplasticity, personality has a causal effect on the clinical course and outcome of depression; e.g., individual personality determines how patients recover from depression [7]. However, the association between depression and temperament is more complex, and the depressive state also leads to higher HA [5]. In addition, in this patient sample RD also showed potential state-dependent alterations [16], and increase in SD seems to be associated with recovery from depression [26]. Because depressive symptoms have been shown to alter temperament and character profiles, the six-week TCI-R assessments were considered as better representing the patients' long-term temperament and character profiles and were used in the GLM analyses as explanatory variables.

Due to the naturalistic setting we had more lenient inclusion criteria in this study than in other studies with depressed patients, and because of that our patient sample likely included more patients with different subtypes of depressive symptomatology [16]. The patients in this study also had marked comorbidities including life-time diagnosis of (hypo)mania in some cases, and a large proportion had AUD. Moreover, the seasonal patterns of depressive symptomatology or personality disorders were not controlled for in the main analysis. Therefore, these results are not directly applicable to “pure” MDD patients but are more easily generalizable to the mixed populations seen in psychiatric secondary services. A few patients had other SUDs (in addition to AUDs) that were not specified but could have had an effect on the personality profile of these patients. However, because of the low number of patients with other SUDs this have not likely affected the results markedly. According to the treatment procedure only a portion of the patients underwent motivational interviewing in addition to behavioral activation therapy, and, although temperament is considered to reflect relatively stable traits, it is possible that this difference in treatment affected the results. Dropout in follow-up was linked with high AUDIT and low SD at baseline, which may also have affected the results.

4.3. Conclusions

Possibly due to the modifying effect of alcohol use problems, high Reward Dependence was associated with better anti-depressive treatment outcome at 6 months. Harm Avoidance and Self-Directedness did not predict depression outcome when alcohol use problems were controlled.

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Research paper

Temperament clusters associate with anxiety disorder comorbidity in depression

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ABSTRACT

Background: Individual temperament is associated with psychiatric morbidity and could explain differences in psychiatric comorbidities. We investigated the association of temperament profile clusters with anxiety disorder comorbidity in patients with depression.

Methods: We assessed the temperament of 204 specialized care-treated depressed patients with the Temperament and Character Inventory (TCI-R) and their diagnoses with the Mini International Neuropsychiatric Interview. Two-step cluster analysis was used for defining patients' temperament profiles and logistic regression analysis was used for predicting different anxiety disorders for various temperament profiles.

Results: Four temperament clusters were found: 1) Novelty seekers with highest Novelty Seeking scores (n = 56),2) Persistent with highest Persistence scores (n = 36), 3) Reserved with lowest Novelty Seeking scores (n = 66) and 4) Wearied with highest Harm avoidance, lowest Reward Dependence and lowest Persistence scores (n = 58). After adjusting for clinical variables, panic disorder and/or agoraphobia were predicted by Novelty seekers' temperament profile with odds ratio [OR] = 3.5 (95% confidence interval [CI] = 1.8 − 6.9, $p < 0.001$), social anxiety disorder was predicted by Wearied temperament profile with OR = 3.4 (95% CI = 1.6 − 7.5, p = 0.002), and generalized anxiety disorder was predicted by Reserved temperament profile with OR = 2.6 (95% CI = 1.2 − 5.3, p = 0.01).

Limitations: The patients' temperament profiles were assessed while displaying depressive symptoms, which may have affected results.

Conclusions: Temperament clusters with unique dimensional profiles were specifically associated with different anxiety disorders in this study. These results suggest that TCI-R could offer a valuable dimensional method for predicting the risk of anxiety disorders in diverse depressed patients.

1. Introduction

The comorbidity between depressive and anxiety disorders is marked and co-occurrence of more than one disorder is more of a rule than an exception (Brown et al., 2001; Melartin et al., 2002). In clinical populations, comorbidity proportions of different anxiety disorders in major depressive disorder (MDD) vary from 2% to 41% and co-occurrence of at least two different anxiety disorders vary from 36% to 64% between different disorders (Brown et al., 2001). Comorbid anxiety disorders can lead to increased treatment resistance and chronic depression (Burcusa and Iacono, 2007; Holzel et al., 2011) and better comprehension of the etiology of these disorders could enable development of more efficient treatments than currently available ones. The present categorical classification system of psychiatric disorders has been criticized because of a high rate of comorbidity of different diagnoses (Naragon-Gainey et al., 2016). Certain temperamental traits have been suggested to be contributors of a dimensional diagnostic model because they could account for shared symptomatology in both depression and anxiety disorders (Barlow and Kennedy, 2016; Craske and Waters, 2005).

Whereas human temperament is generally associated with individual life choices and behavior (Al-Halabi et al., 2010; Bereczkei and Czibor, 2014; Campbell et al., 2013; El Sheikh et al., 2014; Otani et al., 2008), skewed temperament profile is also associated with psychiatric

Abbreviations: MDD, major depressive disorder; TCI-R, Temperament and Character Inventory; NS, Novelty Seeking; HA, Harm Avoidance; RD, Reward Dependence; P, Persistence; PDA, panic disorder or/and agoraphobia; SAD, social anxiety disorder; GAD, generalized anxiety disorder; MADRS, Montgomery-Åsberg Depression Rating Scale; AUDIT, Alcohol Use Disorder Identification Test; MINI, The Mini International Neuropsychiatric Interview

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disorders (Miettunen and Raevuori, 2012). The most important model developed from the clinical point of view and in part based on biological studies for characterizing human temperament is the psychobiological model of temperament and character (Cloninger, 1986; Cloninger et al., 1993). According to this model, human temperament is largely heritable and is a relatively stable part of personality. Human temperament is considered to present a precognitive bias reflected as individual tendency to 1) avoid possible adverse or threatening situations (Harm Avoidance, HA), 2) participate in events and activities for the sake of novelty and thrill (Novelty Seeking, NS), 3) seek social approval of others (Reward Dependence, RD), and 4) be persistent in ones efforts, even in the absence of imminent rewards (Persistence, P) (Cloninger et al., 1993). Although the associations between temperament and affective disorders are most likely complex (Klein et al., 2011), certain temperament traits could predispose to psychopathology via disadvantageous cognitions (e.g., rumination) (Mezulis et al., 2011) and behaviors (e.g., avoidant behavior or excessive reassurance seeking) (Cheavens and Heiy, 2011; Kanter et al., 2008; Weinstock and Whisman, 2007).

The temperament trait 'high HA' is associated with MDD and all anxiety disorders. HA and depression severity are positively correlated and social phobia or social anxiety disorder (SAD) appear to be associated with higher levels of HA than other anxiety disorders (Kampman and Poutanen, 2011; Kampman et al., 2014; Miettunen and Raevuori, 2012). Indeed, the trait 'high HA' could be an important common etiological factor for depression and anxiety, and according to Cloninger's original theory, it responds to "obsessional" information-processing type associated with "cognitive anxiety" (Cloninger, 1986). Although Cloninger also postulated that high Novelty Seeking would respond to "histrionic" information-processing type associated with "somatic anxiety", (Cloninger, 1986) studies have not systematically supported associations between this trait and different anxiety disorders. Instead, high NS is associated with substance use disorders (SUDs) and dual diagnosis (Fernandez-Mondragon and Adan, 2015; Howard et al., 1997; Sher et al., 2000), whereas intermediate and low levels of NS have been found in panic disorder and in SAD, respectively (Kampman et al., 2014; Miettunen and Raevuori, 2012). The trait 'high RD' could be associated with panic disorder, but the results are incongruent, with different directions observed for the association between genders (low RD for women and high RD for men) (Kampman et al., 2014; Starcevic et al., 1996). In patients with social anxiety disorder, results regarding RD have also been mixed and are on average at an intermediate level according to one meta-analysis (Kampman et al., 2014). For P patients with anxiety disorders, intermediate scores have generally been observed, while low scores have shown to be associated with social phobia and alcohol dependence among patients without anxiety disorders (Kampman et al., 2014; Miettunen and Raevuori, 2012; Rae et al., 2002). GAD has been associated with high HA and impulsive symptoms in patients with GAD could be associated with high NS and low RD (Kampman et al., 2014; Piero, 2010).

Although meta-analytic data exist on the association between separate temperament dimensions and different anxiety disorders, no studies have investigated the impact of temperament clusters on occurrence of anxiety disorders. Individual profile data on all temperament dimensions have been suggested to possibly offer more comprehensive information of the association between temperament and different anxiety disorders (Miettunen and Raevuori, 2012). In this study, we aim to explore if temperament profiles determined with cluster analysis are associated with the likelihood of anxiety disorders (panic disorder and/or agoraphobia [PDA], social anxiety disorder and generalized anxiety disorder) in a sample of depressed patients.

2. Methods

2.1. Participants

In brief, the study group comprised 242 patients who were referred to psychiatric services because of depressive symptoms, anxiety, self-destructiveness, insomnia or substance-related problems. Patients scoring a minimum of 17 points on the Beck Depression Inventory (BDI, version 1A, (Beck et al., 1996) and thus reflecting at least a moderate level of depressive symptoms, were included in the study. Patients with organic brain disease or psychotic (ICD-10 F2*) disorder were excluded from the study. A description of the study protocol and the screened patient sample has been presented elsewhere (see ClinicalTrials.gov Identifier NCT02520271, Ostrobothnia Depression Study [ODS], 2017 and (Paavonen et al., 2016)). Up to 38 (15.7%) patients dropped out from the study after enrollment, and 204 patients (out of which 120 (59%) were women) were included in the final analysis. Sociodemographic data, MADRS and AUDIT-C scores of the patient sample are available as supplementary electronic background material.

2.2. Procedures

Included patients completed the forms for the following assessments: The Temperament and Character Inventory (TCI-R) (Cloninger et al., 1993), and Alcohol Use Disorders Identification Test (AUDIT-C [questions 1–3 of AUDIT questionnaire]) (Bohn et al., 1995). Sociodemographic data were also collected. The clinical evaluation included the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the Mini International Neuropsychiatric Interview 5.0 (MINI) (Sheehan et al., 1998), and patients' medication was also evaluated. The antidepressant doses prescribed to each patient were converted to fluoxetine equivalents for enabling comparison of prescribed antidepressants between different patient groups, which has been described in further detail elsewhere (Paavonen et al., 2016).

According to the MINI, 181 patients (88.7%) met the criteria for MDD, 17 (8.3%) for dysthymia, 25 (12.3%) for hypomanic episode (lifetime), 49 (24%) for panic disorder, 35 (17.2%) for agoraphobia, 40 (19.6%) for social anxiety disorder, 68 (33.3%) for generalized anxiety disorder, 15 (7.4%) for obsessive compulsive disorder, 15 (7.4%) for post-traumatic stress disorder, 66 (32.4%) for alcohol use disorder, 10 (4.9%) for other substance use disorder and 5 (2.5%) for bulimia. Comorbidity of disorders was marked and 150 (74%) patients were diagnosed with at least two disorders. As was expected, co-occurrence of panic disorder and agoraphobia was marked and 69 (33.8%) patients had either panic disorder or agoraphobia or both. An overlap was also observed for GAD with other anxiety disorders (PD, AP, OCD, SAD, PTSD) and 41 patients (20.1%) had GAD without these comorbidities. In this study, we focused on the four most prevalent anxiety disorders in the sample: panic disorder and/or agoraphobia (PDA), SAD and GAD.

2.3. Ethical issues

The study was approved by the local Human Subjects Review Committee and participants gave their informed written consent. All included patients were evaluated as having the capacity to give informed consent because patients with psychotic and organic brain diseases were excluded. For further information, see ClinicalTrials.gov Identifier (NCT02520271).

2.4. Statistical methods

A two-step cluster analysis was used for defining patients' temperament profiles. This method allows handling of large data sets by first identifying groupings with quick cluster algorithm (pre-clustering) and it runs hierarchical cluster models in the second step. Temperament

Table 1
Clinical characteristics and distributions of anxiety disorders and their differences between the four temperament clusters (Novelty seekers).

			Clinical variables				Diagnoses		
Temperament clusters	Age * (mean ± SD)	Male gender (*n*, %)	Antipsychotics in use	Antidepressant dose (mean ± SD)	AUDIT-C scores (mean ± SD)	MADRS scores (mean ± SD)	PDA (*n*, %)	SAD (*n*, %)	GAD (*n*, %)
1. Novelty seekers (*n* = 56, 26%**)	36.7 ± 12.5	29, 51.8%	16, 28.6%	27.2 ± 21.4	5.64 ± 3.64	22.4 ± 6.6	28, 54.9%	10, 19.6%	7, 13.7%
2. Persistent (*n* = 36, 17%**)	42.5 ± 12.2	12, 33.3%	7, 19.4%	25.2 ± 18.7	4.31 ± 3.43	23.1 ± 7.7	5, 14.3%	1, 2.9%	8, 22.9%
3. Reserved (*n* = 66, 30%**)	41.4 ± 11.6	22, 33.3%	15, 22.7%	25.0 ± 21.0	4.39 ± 3.29	22.6 ± 6.1	14, 22.2%	10, 15.9%	20, 31.7%
4. Wearied (*n* = 58, 27%**)	34.8 ± 11.4	25, 43.1%	22, 37.9%	32.4 ± 19.2	4.93 ± 3.24	24.5 ± 5.4	22, 40.0%	19, 34.5%	6, 10.9%
Difference between the clusters									
χ^2		5.28	5.08				**20.81**	**14.57**	**9.67**
p	**0.003**[a]	0.15[b]	0.166[b]	0.18[a]	0.16[a]	0.26[a]	**<0.001**[b]	**0.002**[b]	**0.02**[b]

Persistent, Reserved and Wearied).
Abbreviations: AUDIT-C = Alcohol use disorder identification test (questions 1–3); PDA = Panic disorder and/or Agoraphobia; SAD = Social anxiety disorder; GAD = Generalized anxiety disorder.
Percentages in clinical variables and diagnoses are proportions of the temperament clusters.
*Differences were significant between clusters 2 and 4, and between clusters 3 and 4 in Bonferroni analysis.
**Proportion of the whole patient sample.
Significant differences are in boldface.
[a] For ANOVA between the temperament clusters.
[b] For chi-square between the temperament clusters.

dimension scores of NS, HA, RD and P were used in the cluster model. Number of clusters were set to automatic for achieving natural clustering.

The differences in discrete variables (age, antidepressant dose, AUDIT-C score and MADRS score) between temperament clusters were calculated with ANOVA. Differences between grouping variables (gender, the use of antipsychotics, and diagnoses) were calculated with χ^2-statistics.

To adjust for possible confounding variables (age, gender, depression severity and alcohol use) binary logistic regression models were used for predicting the following diagnoses: 1) panic disorder and/or agoraphobia (PDA), 2) social anxiety disorder (SAD) and 3) generalized anxiety disorder (GAD). The diagnoses were predicted with the temperament cluster which had the highest prevalence of the dependent diagnosis (these prevalences are reported in Table 1.) and the models were adjusted with 1) age and gender in Model 1, 2) age, gender and MADRS scores in Model 2, and 3) age, gender, MADRS and AUDIT-C scores in Model 3. The used explanatory (binary) temperament cluster variables were: 1) Novelty seekers cluster vs. others in models predicting PDA, 2) Wearied cluster vs. others in models predicting SAD, and 3) Reserved cluster vs. others in models predicting GAD. All analyses were performed with SPSS for Mac (version 24.0, IBM Inc. Armonk, New York, USA).

3. Results

Based on TCI-R temperament dimension scores, the two-step cluster analysis produced four temperament clusters with fair overall quality. After their assessment, these four temperament clusters were named with descriptive labels according to the temperament profile reflecting the combination of scores in different temperament dimensions: 1) Novelty seekers with highest NS, $n = 56$, (NS = 119.4 ± 9.0, HA = 111.0 ± 14.2, RD = 103.3 ± 13.5, P = 98.0 ± 15.5; mean ± SD), 2) Persistent with lowest HA and highest P, $n = 36$, (NS = 99.6 ± 17.1, HA = 87.3 ± 11.0, RD = 107.9 ± 15.6, P = 125.0 ± 12.6), 3) Reserved with lowest NS, $n = 66$, (NS = 88.1 ± 12.3, HA = 119.9 ± 11.5, RD = 104.5 ± 14.6, P = 105.4 ± 15.6), and 4) Wearied with highest HA and lowest RD and P, $n = 58$, (NS = 95.7 ± 10.4, HA = 129.8 ± 14.8, RD = 84.7 ± 14.3, P = 82.4 ± 15.3) (Fig. 1).

No differences were observed between the temperament clusters in gender distribution, depression severity, alcohol use or in the use of antipsychotics or prescribed antidepressant doses (Table 1). Persistent and Reserved patients were younger compared with Wearied patients. The Persistent cluster had the lowest occurrence of all anxiety disorders and PDA was most prevalent in Novelty seekers, SAD in Wearied and GAD in Reserved. The prevalence of different diagnoses in each of the temperament clusters of and χ^2 and *p* values for the differences in the occurrence of the disorders between clusters are presented in the Table 1.

The Novelty seekers cluster had higher odds (odds ratio [OR] = 3.28–3.52, $p \leq 0.001$) for PDA compared with other patients in the three logistic regression models adjusted with 1) gender and age, 2) gender, age and depression severity, and 3) gender, age, depression severity and alcohol use. In the three models explaining SAD, the Wearied cluster had higher odds (OR = 3.17 − 3.41, $p = 0.002 - 0.003$) for SAD compared with other patients and in the three models explaining GAD, the Reserved cluster had higher odds (OR = 2.53 − 2.60, $p = 0.009 - 0.01$) for GAD compared with the other patients. The results of these regression models are presented in Table 2.

4. Discussion

Our main findings were that Novelty seekers, Reserved and Wearied temperament clusters were uniquely associated with different anxiety

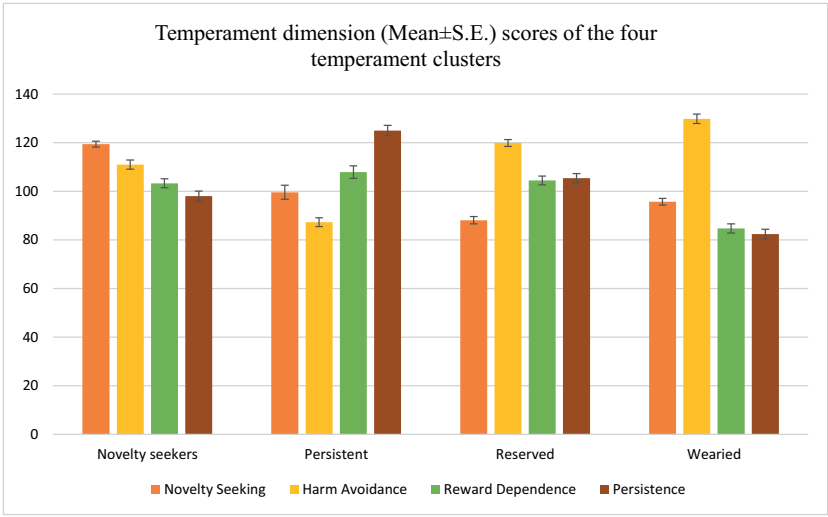

Fig. 1. Temperament dimension (Mean ± S.E.) scores of the four temperament clusters.

disorders, whereas the Persistent temperament cluster was associated with significantly lower prevalence of anxiety disorders. More specifically, panic disorder and/or agoraphobia were predicted by the Novelty seekers temperament, social anxiety disorder by Wearied temperament and generalized anxiety disorder by Reserved temperament in this sample of diverse depressed patients.

4.1. Panic disorder and agoraphobia

Panic disorder and/or agoraphobia were most highly prevalent in the Novelty seekers cluster, and their lowest occurrence was observed in the Persistent cluster. Considering the specifications of panic disorder and agoraphobia in the Diagnostic and Statistical Manual of mental disorders (DSM-IV-TR (2000) 4th ed., text rev.), these disorders likely associate with both types of anxiety defined in Cloninger's original theory, namely cognitive and somatic, with panic attacks responding to somatic anxiety and continuous concern of attacks or agoraphobia to cognitive anxiety. Thus, the anticipated result was that the highest prevalence of PDA would be observed in the Novelty seekers cluster, which was characterized by highest scores in NS (presumably associated with somatic anxiety) and above the population norm in HA (presumably associated with cognitive anxiety) (Jylhä and Isometsä, 2006). In the logistic regression models (adjusted with depression severity, alcohol use, age and gender), the odds for PDA for Novelty seekers were over three times as high as that for other patients, thereby suggesting a strong association between the Novelty seekers temperament profile and panic disorder. Earlier evidence has mainly suggested no associations between the trait 'high NS' and panic disorder comorbidity in depressed patients and one earlier study has found an inverse relation between the two (Ampollini et al., 1999; Kennedy et al., 2001; Ongur et al., 2005). However, these studies likely included patient samples with less variance in NS compared with our sample due to excluding patients with substance use disorders (Ampollini et al., 1999; Kennedy et al., 2001; Ongur et al., 2005), who 1) are likely to have higher NS scores (Howard et al., 1997) and 2) have a high predisposition to panic disorder (Zvolensky et al., 2006). This difference in samples could explain our novel finding of a strong association between Novelty seekers temperament (with high NS) and higher risk for panic disorder.

Neuropsychologically the increased morbidity in panic disorder and agoraphobia in Novelty seekers could be associated with aberrant functioning in paralimbic brain areas that are associated with both

Table 2
Likelihood of anxiety disorders (PDA, SAD and GAD) according to the temperament clusters in the logistic regression models.

	PDA				SAD				GAD			
	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*
		lower	upper			lower	upper			lower	upper	
Model 1												
Temperament cluster*	3.28	1.67	6.41	0.001	3.17	1.49	6.76	0.003	2.60	1.27	5.33	0.009
Model 2												
Temperament cluster*	3.52	1.78	6.96	< 0.001	3.19	1.47	6.90	0.003	2.53	1.23	5.21	0.01
Model 3												
Temperament cluster*	3.48	1.76	6.91	< 0.001	3.41	1.55	7.49	0.002	2.55	1.24	5.27	0.01

Model 1: adjusted with gender and age.
Model 2: adjusted with gender and age, and MADRS scores.
Model 3: adjusted with gender, age, MADRS scores and AUDIT-C scores.
*Binominal variables: 1) Novelty seekers cluster vs. others explaining PDA, 2) Wearied cluster vs. others explaining SAD, and 3) Reserved cluster vs. others explaining GAD.
Abbreviations: PDA = Panic disorder and/or agora phobia; SAD = Social anxiety disorder; GAD = Generalized anxiety disorder; MADRS = Montgomery Åsberg depression rating scale; AUDIT-C = Alcohol use disorder identification test (questions 1–3), OR = odds ratio, CI = confidence interval.

Novelty Seeking and panic disorder (De Cristofaro, et al, 1993; Sugiura et al., 2000). These brain areas including right anterior cingulate cortex and anterior/posterior insula constitute in part networks associated with interoceptive functions and with panic disorder (Cui et al., 2016; LeDoux and Pine, 2016; Sugiura et al., 2000). Psychological theories have also suggested that interoceptive functions (e.g. interoceptive conditioning and/or catastrophic misappraisals of bodily sensations) are central in the etiology of panic attacks and panic disorder (Bouton et al., 2001; Craske and Waters, 2005). High Novelty Seeking could be a moderator of the association between interoceptive functions and panic disorder hypothetically via "histrionic" information processing style (Cloninger, 1986). This kind of moderating effect would be in line with our finding of highest prevalence of PDA in patients with a temperament profile including the highest NS scores (Novelty seekers) and significantly lower prevalence in patients with a temperament profile including the lowest NS scores (Reserved).

Earlier studies have shown that panic disorder is associated with high HA (Kampman et al., 2014), and in addition to high NS observed in Novelty seekers, increased HA could be an important part of this temperament profile, thus explaining the high prevalence of panic disorder (and SAD) found in this patient group.

4.2. Social anxiety disorder

The highest prevalence of social anxiety disorder was observed in the Wearied cluster and the lowest in the Persistent cluster. After adjusting with clinical variables, the Wearied temperament profile, characterized by highest HA and lowest RD and P, predicted SAD in the regression models with a higher odds that was over three times as high as that for other patients. Earlier evidence has shown that high HA is associated with all anxiety disorders with highest levels found in SAD, which is well in line with our finding of Wearied cluster patients (having the highest HA) having the high prevalence of different anxiety disorders and the highest prevalence of SAD (Kampman et al., 2014; Miettunen and Raevuori, 2012). HA is also associated with severity of depressive symptoms and all these findings together suggest that the highest scores in HA are associated with SAD and more severe depression (Kampman and Poutanen, 2011). According to high HA's definition, this trait is associated with avoidant behavior and according to Cloninger's original theory, high HA is also associated with obsessional information processing type (Cloninger, 1986,1987). These kinds of behavioral avoidance and cognitive unconstructive repetitive thinking patterns could be the link between high HA and both SAD and depression (Kanter et al., 2008; Watkins, 2008; Weinstock and Whisman, 2007). This would lead to interpreting the preceding findings as suggesting that more severe depression and SAD are more strongly associated with avoidance and ruminative or repetitive thinking patterns compared with other anxiety disorders. This kind of common etiological factor could explain the higher comorbidity rate of SAD compared with other anxiety disorders in MDD patients (Brown et al., 2001) and suggest that the etiology of SAD resembles more to that of severe depression than other anxiety disorders in these cognitive and behavioral aspects. As negative mood valent rumination is associated with heightened neural activity in default mode network (Graham et al., 2013; Malhi et al., 2015), high HA could be linked to depression via similar neuropsychological mechanisms.

Negative affectivity or neuroticism, which represent traits similar to HA (Capanna et al., 2012), have been proposed by earlier studies as posing a higher-order personality trait common to depressive and anxiety disorders and that other unique factors differentiate between separate disorders (Clark and Watson, 1991; Craske and Waters, 2005). Although the highest scores of HA could be associated especially with SAD and more severe depression, as discussed in a previous paragraph, HA is likely to also present more general factors predisposing to psychopathology, similarly to neuroticism (Kampman and Poutanen, 2011; Kampman et al., 2014; Miettunen and Raevuori, 2012). Moreover, our results suggest that emotional detachment and low ambition (reflected as lower RD and P in the Wearied patients' temperament profile) compared with other patients could be an important distinctive characteristic of this temperament profile associated specifically with higher risk for SAD.

4.3. Generalized anxiety disorder

Generalized anxiety disorder had the highest prevalence in the Reserved cluster and the lowest in the Persistent cluster. GAD was predicted by the Reserved temperament profile in the regression models with over two times as high odds than that of other patients. Reserved patients were characterized by lowest NS, high HA, and had RD and P traits roughly corresponding to those observed in the Finnish general population (Jylhä and Isometsä, 2006). Evidence of the associations between temperament and GAD is scarce, but the main finding has been in line with our results, with GAD suggested to be associated with high HA (Kampman et al., 2014). In addition to this, our results suggest that low NS could be an important part of the temperament profile associated with GAD even though a similar association has not been found previously (Ongur et al., 2005; Piero, 2010). As discussed in chapter 4.1, panic disorder is suggested to be associated with interoceptive functions and Novelty seekers temperament profile (with high NS responding to "histrionic" information processing) could be a moderator of this association. Thus, Reserved patients could be at lower risk for panic disorder due to being less affected with "histrionic" or impulsive information processing. Instead, the present results suggest that the proclivity to slow and rigid decision making, slow engagement to new interests or preoccupation in details associated with low NS could predispose these individuals to generalized anxiety when experienced together with other traits predisposing to development of psychopathology, such as high HA (Cloninger, 1987; Miettunen and Raevuori, 2012).

4.4. Persistent temperament profile

The lowest prevalence in all analyzed anxiety disorders was associated with the Persistent cluster which was characterized by highest P and lowest HA when compared to the other temperament clusters. Moreover, the Persistent patients could likely be associated with higher P when compared to general population because markedly lower scores ($P = 114.6 \pm 17.3$) have been found in Finnish general population earlier (Jylhä and Isometsä, 2006). However, the lack of a control group prevents conclusions of the relative differences between these populations. Finding the Persistent patients having lower prevalence of anxiety disorders was a plausible result because high P has been associated with positive emotionality and well-being (Cloninger et al., 1998; Garcia, 2011), especially together with low HA and character trait low Self-Directedness (Cloninger et al., 2012). Our results are in line with these findings and support a hypothesis that the combination of low HA and high P associates with lower comorbidity of anxiety disorders in depressed patients.

4.5. Strengths and limitations

Because individual temperament presents a precognitive bias resulting in different behaviors, the cluster analysis provided complete temperament profiles reflecting more comprehensively the individual, temperament-oriented behavior in patients. Although meta-analytic data exist on how different temperament traits are uniquely predisposing to different affective disorders, it was important to test the hypothesis of whether individual complete profile data (in terms of temperament clusters) predict the occurrence of anxiety disorders in depressed patients. Moreover, it is possible that these temperament clusters would reflect endophenotypes predisposing to different disorders because they were associated with different disorders in this

study. These kinds of endophenotypes could be more closely associated with the biological background of psychiatric symptoms compared with categorical diagnoses or separate temperament traits and could help in the progress of finding biomarkers for psychopathology (Service et al., 2012). Testing the possible associations between temperament clusters and candidate genes of anxiety disorders would be interesting in future studies (Sharma et al., 2016).

Although the temperament profiles of the studied four temperament clusters showed strong associations with different anxiety disorders, the lack of a control group in the study posits some limitations that have to be considered when interpreting the results. Firstly, the four temperament clusters may or may not be a unique feature of depressed populations and studies with non-depressed controls are needed to give more insight on this question. Secondly, the patients' temperament profile was assessed during depressive symptoms and may not represent their long-term temperament profile because depressive states are known to be associated with elevation in temperament trait Harm Avoidance (Kampman and Poutanen, 2011). However, the main focus of this study was to evaluate the associations between temperament clusters and the occurrence of anxiety comorbidities. In these analyses the depression severity was controlled for to avoid the bias towards higher risk of comorbidities with more severe depression. Thirdly, because of the high level of comorbid disorders in our sample it is also possible that the current finding of the four temperament clusters is specific for depression with anxiety disorder and substance use comorbidities. Moreover, although human temperament is considered relatively stable over one's life-span (Cloninger et al., 1993) and the temperament clusters predicted specifically higher risk for different anxiety disorders in this study, the cross-sectional setting does not allow interpretations of the possible causal relations between the temperament profiles and the studied anxiety disorders. Longitudinal studies in general population are needed for making conclusions of the possible causality and could have more marked clinical implications compared to studies with cross-sectional settings. Due to the study design using cluster analysis for creating temperament clusters and aiming at analyzing their associations with anxiety disorders, we had no a priori hypotheses in this study, which may also be considered to be a limitation. The use of a semi-structured MINI interview (based on the DSM-IV) could have resulted in overdiagnosing the patients with SAD and PDA because no exclusion criteria according to the hierarchy of these diagnoses were used. However, the diagnosis of GAD was excluded in cases of any other anxiety comorbidities. We combined patients with panic disorder and/or agoraphobia into one group (PDA), which limits the generalizability of these results to clinical settings. Moreover, when interpreting the results, it must also be noted that 25 patients had undergone a previous hypomanic episode, which limits the generalizability of these results to MDD patients. Instead, the results reflect more of the associations between temperament profiles and more diverse patients with current depressive symptoms.

5. Conclusions

Temperament clusters with unique dimensional profiles were specifically associated with different anxiety disorders in this study. These results suggest that TCI-R could offer a valuable dimensional method for predicting the risk of anxiety disorders in diverse depressed patients.

Conflicts of interest

None.

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Supplementary materials

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