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ABSTRACT

Although depression is a long-known and common disease causing serious suffering, its biological etiology is still poorly understood. We understand, as a result of pharmacological studies, the relevance of the serotonin system. Special interest has focused on the presynaptic serotonin transporter (SERT); blocking it is the most common mechanism of antidepressants. In addition to the information gathered from pharmacological research, the significance of the SERT has been evident in studies combining genetics and environmental factors. Indirect evidence has also accumulated from studies of endophenotypes mediating vulnerability to depression. Mechanisms affecting the risk of depression include the reactivity of the limbic system, and the connections of the frontal cortex and the limbic system. Studies that combine SERT genetics and brain imaging have been especially influential in this aspect. Despite our knowledge of the important role of the SERT in depression, basic research especially with drug-naïve subjects is sparse. The role of the SERT in depression is still obscure.

In the first part of the thesis, SERT availability in the midbrain and medial prefrontal cortex was compared in healthy controls and patients with major depression. In the second part, the effect of allelic variation of the long promoter of the serotonin transporter (5-HTTLPR) on SERT availability was assesed in the same brain regions. The third part of the thesis concentrated on examining associations of clinical variables and neuroimaging during both psychodynamic psychotherapy and waiting for psychotherapy. The first study included 29 patients with major depression and 19 age- and sex-matched healthy control subjects. The genetic study had 23 patient participants. In the follow-up study, after the exclusion process and drop-outs, the 33 remaining patients were randomized in two groups. One started psychodynamic psychotherapy immediately and the other waited six months before starting treatment. At the end of the first year of treatment, 24 subjects remained in the study.

SERT availability was imaged with Single Photon Emission Tomography (SPET) using the [123I] nor-β-CIT ligand. Psychiatric diagnoses were aided by an SCID interview. Depression symptoms were assessed with multiple scales, such as BDI, HAM-17, and MADRS. Overall psychiatric symptoms were measured with the Symptom Check List (SCL).

SERT availability in the midbrain decreased in depression. Second, due to the small sample size, the preliminary finding was the effect of 5-HTTLPR on SERT availability in the prefrontal cortex. Depressed patients homozygous for the lower SERT-expressing S-allele had decreased SERT availability in the medial prefrontal cortex, compared to other patients. In the follow-up study, baseline symptom severity correlated with change in SERT availability during both psychodynamic psychotherapy and waiting for therapy. Those patients with more severe symptoms had a higher increase of SERT availability during the follow-up. Clinical changes and neuroimaging changes, however, had no correlation with each other.

Despite the significant difference in SERT availability found between depressed patients and healthy controls, SERT imaging is unsuitable as a diagnostic procedure due to the substantial overlap of the results of depressed and healthy individuals. Symptom severity lacks correlation with SERT availability.

These results provide new information on the role of the SERT in depression. The decrease of SERT availability in depression was confirmed. This mechanism is functionally similar to the action of antidepressant drugs that inhibit serotonin re-uptake. SERT function is affected by genes and environmental factors and seems to be associated with mechanisms of emotional regulation. On the other hand, the SERT may have a compensatory role connected with resilience under stress. The correlation of SERT change and baseline symptom severity is an indirect evidence of the role of the SERT in depression and may be associated with the possible compensatory role of SERT availability in depression.

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Medical Subject Headings: Depressive Disorder, Major; Healthy Volunteers; Serotonin; Serotonin Plasma Membrane Transport Proteins; Neuroimaging; Tomography, Emission-Computed, Single-Photon; Psychotherapy, Psychodynamic; Antidepressive Agents; Genotype; Endophenotypes; Brain; Limbic System; Prefrontal Cortex; Follow-Up Studies

Joensuu, Mikko
Sitoutuminen serotoniinin takaisinottoproteiiniin depressiossa. Lääkenaiivien, depressiosta kärsivien henkilöiden yksifotoniemissiotomografiatutkimuksia: vertailu terveisiin koehenkilöihin, genotyypin vaikutus ja seuranta psykodynaamisen psykoterapian aikana.
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TIIVISTELMÄ

Vaikka depressio on pitkään tunnettu, yleinen ja vakavaa kärsimystä aiheuttava sairaus, sen biologinen alkuperä on edelleen monilta osin huonosti tunnettu. Serotoniinijärjestelmän merkitys depressiossa on hahmottunut depression oireita lievittävien lääkkeiden vaikutusmekanismien tutkimuksen kautta. Huomio on kiinnittynyt erityisesti presynaptiseen serotoniinin takaisinottoproteiiniin (SERT), jonka toiminnan estäminen on depressiolääkkeiden yleisin vaikutusmekanismi. Lääketutkimuksen tuottaman tiedon lisäksi SERT:n merkitys depressiossa on havaittu tutkimuksissa, joissa yhdistetään perimän ja ympäristön vaikutuksia. SERT:n merkityksestä on kertynyt epäsuoraa näyttöä myös erilaisten depressiolle altistavien mekanismien eli endofenotyyppien tutkimuksista. Tällaisia sairausriskiin vaikuttavia mekanismeja ovat limbisen järjestelmän reaktiivisuus ja otsalohkon kuorikerroksen ja limbisen järjestelmän yhteydet. Erityisesti SERT:n genetiikkaa ja aivokuvantamista yhdistelevät tutkimukset ovat tuottaneet tällä alalla tärkeää tietoa. Vaikka SERT:lla on jo pitkään tiedetty olevan merkittävä rooli depressiossa, perustutkimus erityisesti lääkkeettömien koehenkilöiden suhteen on ollut vähäistä. SERT:n rooli depression etiologiassa on edelleen epäselvä.

Väitöstutkimuksen ensimmäisessä osatyössä vertailtiin terveiden verrokkien ja keskivaikeasta depressiosta kärsivien henkilöiden keskiaivojen ja sisäpuolisen otsalohkon etuosan SERT-sitoutumista. Toisessa osatyössä arvioitiin SERT:n pitkän promoottorigeenin (5-HTTLPR) alleelivariaation vaikutusta SERT-sitoutumiseen samoilla aivoalueilla. Kolmannessa osatutkimuksessa keskityttiin kliinisten muuttujien ja kuvantamislöydösten yhteyksien selvittämiseen psykodynaamisen psykoterapian ja sen odottamisen aikana.

Ensimmäisen osatyön aineistona oli 29 vähintään keskivaikeaa depressiota sairastavaa potilasta ja 19 ikä- ja sukupuolikaltaistettua tervettä verrokkia. Geneettiseen tutkimukseen osallistui 23 depressiopotilasta. Seurantatutkimukseen poissulkuprosessin ja tutkimuksesta poistuneiden jälkeen jääneet 33 tutkittavaa satunnaistettiin heti psykodynaamisen psykoterapian aloittaneeseen tai puolen vuoden ajan psykoterapiaa odottaneeseen ryhmään. Seurantatutkimuksen ensimmäisen terapiavuoden jälkeen tutkimuksessa oli mukana 24 henkilöä.

SERT-sitoutumista kuvannettiin yksifotoniemissiotomografian (SPET) avulla käyttäen [123I] nor-β-CIT merkkiainetta. Psykiatrisessa diagnostiikassa käytettiin SCID- haastattelua. Depression oireita kartoitettiin käyttäen useita oiremittareita (BDI, HAM-17, MADRS) ja yleistä psykiatrista oireistoa arvioitiin Symptom Chek List:n (SCL) avulla.

Keskiaivojen SERT- sitoutuminen todettiin depressiossa alentuneeksi. Toisena, pienen otoskoon vuoksi, alustavana löydöksenä oli 5-HTTLPR vaikutus otsalohkon aivokuoren SERT-sitoutumiseen. Vähemmän SERT:a tuottavan S-alleelin suhteen homotsygoottisilla depressiopotilailla todettiin muita depressiopotilaita matalampi SERT-sitoutuminen sisäpuolisen otsalohkon etuosan aivokuorella. Seurantatutkimuksessa lähtötilanteen oireiden vakavuusaste korreloi psykodynaamisen psykoterapian ja terapian odotuksen aikaiseen SERT-sitoutumisen muutokseen. Lähtötilanteessa vaikeampioireisten SERT-

sitoutuminen lisääntyi seurannassa enemmän. Oiremuutokset ja kuvantamismuutokset eivät kuitenkaan korreloineet keskenään.

Vaikka SERT- sitoutumisessa nähtiin depressiopotilaiden ja terveiden välillä merkitsevä ero, SERT -sitoutumisen kuvantaminen ei sovellu diagnostiseksi tutkimukseksi johtuen päällekkäisyyksistä depressiopotilaiden ja terveiden koehenkilöiden kuvantamistuloksissa. Depression oireiden vakavuus ei korreloinut SERT-sitoutumiseen.

Löydökset antavat uutta tietoa SERT:n roolista depression etiologiassa. Tutkimus vahvisti SERT sitoutumisen olevan alentunut depressiopotilailla. Depressiossa alentunut SERT-sitoutuminen voidaan toiminnallisesti rinnastaa yleisesti depression hoidossa käytettyjen lääkkeiden serotoniinin takaisin ottoa estävään vaikutusmekanismiin. SERT:n toiminta on geenien ja ympäristön säätelemää ja se näyttäisi liittyvän depressiolle altistaviin tunnesäätelyn mekanismeihin. Toisaalta SERT:lla saattaa olla kompensatorinen ja stressiin sietoon liittyvä rooli. SERT-muutoksen korrelaatio lähtötilanteen oirekuvan vakavuuteen on epäsuora osoitus SERT:n roolista depressiossa ja saattaa liittyä depressiossa matalan SERT- sitoutumisen kompensatoriseen rooliin.

Luokitus: QV 126, WM 171.5, WM 420, WN 206, QU 500
Yleinen suomalainen asiasanasto: masennus; serotoniini; tomografia; yksifotoniemissiotomografia; psykodynaaminen psykoterapia; geenit; genotyyppi; fenotyyppi; psyykenlääkkeet; välittäjäaineet; aivot; aivokuori; seurantatutkimus

FOREWORD/ACKNOWLEDGEMENTS

No more percussion of the heads.

As I was considering specializing in psychiatry, I had a dream. In this dream, I was working in the psychiatric ward of our university clinic and happened to overhear a conversation between the professor and the psychiatric trainees. The professor was telling the trainees not to perform percussion on the heads. (Percussion here means examiners knocking patients with their fingers and interpreting the echoes of the knocks. In reality, this method has probably never been used in psychiatry.) In my dream, however, according to the professor, the tradition of percussion endangered the credibility of psychiatric faculty.

I believe this dream reflected both the curiosity and fears that I had in mind entering the largely unmapped territory of psychiatry. I was, from the beginning, very much drawn towards views trying to combine psychological and biological understanding of the mind.

This dream attracted me to undertake a difficult and ongoing journey. I guess concentrating on one and the same mission for a long time has never been my strongest quality. It is easier to come up with interesting topics and to get carried away with new ideas than it is to carefully explore one and to do all the necessary paperwork and formalities associated with research work. Despite many moments of frustration, procrastination, and regret, this thesis has offered me a great opportunity to get familiar with one narrow area of biological psychiatry and to work with a fascinating group of colleagues and psychotherapists. The integrative and holistic view of psychiatry and respect of all aspects of the human mind in the research team has always been a source of inspiration for me.

Growing to be smaller

I started with global interest in the connections of material biological structure and immaterial psychological conceptualizations. During the work, however, the complexities of both worlds forced me to realize that the integrative vision of the mind can grow and improve only through multiple small glimpses through narrow keyholes of research. Instead of trying to solve mind-blowing mysteries, being able to work in a team providing data accepted by the research community as a small part of a large ever-evolving puzzle is a source of great gratification.

Clinical aspects

I worked several years as a psychiatrist in a mood disorder-focused group in an outpatient clinic, and I met numerous patients with depression and anxiety. Currently, however, I am working in a ward of forensic psychiatry with patients who, in addition to psychotic disorder, have a personality disorder–in some cases, with several features of psychopathy. Thus, I have had the possibililty to observe highly contrasting groups of patients: some highly emotional and vulnerable and others extremely cold and resilient to depression. I find both this contrast in emotional reactiveness and accumulating knowledge of underlining mechanisms fascinating.

Acknowledgements

In many sports, the clock tells the truth. In this thesis process, the calendar clearly indicates that there has been a great amount of difficulty in my labour. The nature of those obstacles would most probably warrant a more thorough examination of my own head, which has served as a so-called healthy control in neuroimaging. Without going into more detail and rumination on this subject, I can state that I have needed a lot of encouragement and “kicks on the ass” during this work.

These studies would not have been possible without the depressed and healthy study subjects. Thank you all for your helpfulness and patience. I want to openly thank professor Lehtonen for all the guidance and coaching and especially tolerance throughout this lengthy process. I also want to thank my two other supervisors, Minna Valkonen-Korhonen and Jari Tiihonen, for their comments and thoughts, thus helping me identify the focus of the work. All the members of our research team: Pirjo Saarinen, Pasi Ahola, Tommi Tolmunen, Soili Lehto, and Pertti Hella, deserve dearest thanks for all the help they have given. I want to express special thanks to Pasi for numerous discussions as we were both taking unsure steps in the field of science. When we had difficulty dealing with our data, we got, through professor Lehtonen, new allies

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Finally, I want to thank those who had to observe this process from a close distance. Those who heard the greatest numbers of complaints and those who had to encourage me when I was about to give up. Thanks to all my family members and friends.

Szeged, June 25, 2019

LIST OF THE ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:

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II Joensuu M, Lehto S M, Tolmunen T, Saarinen P I, Valkonen-Korhonen M, Vanninen R, Ahola P, Tiihonen J, Kuikka J, Pesonen U, Lehtonen J. Serotonin-transporter-linked promoter region polymorphism and serotonin transporter binding in drug-naïve patients with major depression. Psychiatry Clin. Neurosci 64: 387-393, 2010.

III Joensuu M, Ahola P, Knekt P, Lindfors O, Saarinen P, Tolmunen T, Valkonen-Korhonen M, Vanninen R, Jääskeläinen T, Virtala E, Tiihonen J, Lehtonen J. Baseline symptom severity predicts serotonin transporter change during psychotherapy in depression. Psychiatry Clin. Neurosci 2016; 70: 34–41.

CONTENTS

ABBREVIATIONS

[123I]	nor-β-CIT
[(123)I]-nor-beta-CIT	(2beta-carbomethoxy-3beta-(4-iodophenyl)tropane)
5-HIAA	5-Hydroxyindoleacetic Acid
5-HT	Serotonin
5HT1A	Presynaptic Serotonergic Autoreceptor 1A
5-HT2A	Presynaptic Serotonergic Autoreceptor 2A
5-HTP	5-hydroxytryptamine
5-HTTLPR	Serotonin Transporter Long Promoter
ACTH	Adreno Corticotropic Hormone
AKT	Protein kinase B
BDI	Beck Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
CAR	Cortisol Awakening Response
CNS	Central Nervous System
CREB	cAMP Response Element Binding Protein
CSF	Cerebrospinal Ffluid
CT	Computer Tomography
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DEPS	Depression Screening Instrument Dex-CRHtest Dexamethasone-Corticotropin Test
DG	Direct Therapy Group
DMN	Default Mode Network
DNA	DeoxyriboNucleic acid
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders Fourth Edition
DSM-V	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ECT	Electroconvulsive Therapy
EEG	Electroencephalography
ERK	Extracellular Signal-Regulated Kinases
fMRI	Functional Magnetic Resonance Imaging
GAD	Generalized Anxiety Disorder
HDRS-17	17-item Hamilton Rating Scale for Depression
HPA	Hypothalamus Pituitary Axis
ICD-10	International Classification of Diseases Tenth Edition
IL-1β	Interleukin 1 β
KELA	The Social Insurance Institution of Finland
L-allele	Long Allelic Variant of the 5-HTTLPR
LTP	Long-Term Potentiation
MAO	Monoamine Oxidase Inhibitor
MAPK	Pp38 Mitogen-Activated Protein Kinase
MDD	Major Depressive Disorder
MDMA	Methylenedioxymethampetamine, "Ecstasy"
Mir-16	Micro RNA-16
MPC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
N2O	Laughing Gas
NARI	Noradrenaline Re-uptake Inhibitors
NF-B	Nuclear Factor Kappa Light-Chain-Enhancer of Activated B Cells
NMDA	N-Methyl-D-Aspartate Receptor
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NORT	Noradrenaline Transporter
NSS	Neurotransmitter Sodium Symporter
PCA	Pp-chloroamphetamine
PCR	Polymerase Chain Reaction
PD	Personality Disorder
PET	Positron Emission Tomography
PFC	Prefrontal cortex
PSA-NCAM	Polysialylated Neuronal Cell Adhesion Molecule
RNA	RiboNucleic Acid
ROI	Region of Interest
rTMS	Repeated Transcranial Magnetic Stimulation
S.D.	Standard Deviation
S-allele	Short Allelic Variant of the 5-HTTLPR
SCID I and II	Structured Clinical Interview for DSM IV diagnosis I and II
SCL-90ANX	Anxiety Scale of the Symptom Checklist
SCL-90-DEP	Depression Scale of the Symptom Checklist
SCL-90-GSI	Global Severity Index of the Symptom Checklist
SERT	Serotonin Transporter
SNP	Single Nucleotide Polymorphism

SNRI	Serotonin and Noradrenaline Reuptake Inhibitor
SPECT	Single Photon Emission Computerized Tomography
SSRI	Selective Serotonin Reuptake Inhibitor
TAS-20	Toronto Alexithymia Scale 20
TCA	Tricyclic Antidepressants
TMS	Transcranial Magnetic Stimulation
TNF	Tumor Necrosis Factor
TrKB	Tyrosine Receptor Kinase B
VNS	Vagal Nerve Stimulation
WG	Waiting Group
WHO	World Health Organization

1 INTRODUCTION

"A light seen suddenly in the storm, snow
Coming from all sides, like flakes
Of sleep, and myself
On the road to the dark barn
Halfway there, a black dog near me."

– Robert Bly, from "Melancholia" in The Light Around the Body (1967).

Depression is a major source of suffering for humankind. Despite long-standing efforts in explaining the pathological mechanisms of depression, many details remain obscure. The relatively young field of psychiatry has experienced strong shifts in the way of thinking, and the division of biological and psychological views has caused controversy. During recent decades, however, novel research methods have yielded knowledge that enables a meaningful integration of some previously contradictory viewpoints. (Moran and Zaki, 2013; Stoyanov et al., 2017; Lehtonen et al., 2012).

Depression has been with us for a long time. The first description of a condition resembling the current definition of depression was adopted by medicine from Greek philosophy by Hippocrates and later Galenos and Avicenna. In their humoral medicine, the concept of "excessive black bile" was used to refer to a condition resembling the current diagnosis of depression (Arikha, 2007).

The fundaments of the biological understanding of the etiology of depression were typically layed first by serendipitious findings and refined through the method of trial and error (López-Muñoz and Alamo, 2009). Still, lack of understanding of the individual needs of depressed patients prolongs the suffering caused by depression. One-size-fits-all solutions are offered when deeper knowledge is unavailable. Scientific debate over the role of serotonin and its reuptake in the etiology and treatment of the disorder has been going on for more than half a century (Coppen, 1967; Cowen 2008; Cowen and Browning, 2015).

Improved understanding of serotonergic synaptic transmission (presynaptic reuptake and postsynaptic receptor binding) and its genetic regulation as well as of pharmacotherapy and the role of non-pharmacological interventions is still needed. Accumulating knowledge is likely to contribute to developing or maintaining prevention and treatment strategies of depression. In the future, individual clinical neuroimaging and genetic testing may allow more accurate diagnosis, possibly allowing tailored choices of pharmacological and non-pharmacological treatment strategies.

As basic research concerning the role of serotonin and its transporter protein SERT is further warranted, this thesis concentrates on the already existing literature on the topic and three neuroimaging studies, aiming to shed some new light on this hot though somewhat old topic.

2 REVIEW OF THE LITERATURE

2.1 DEPRESSION

2.1.1 Definition and diagnosis of depression

Depression is a syndrome. The relevance of psychiatric diagnosis is justified by the typical course of the illness and the typical reaction to different treatments. Most psychiatric disorders lack exact knowledge of etiology, and diagnoses currently cannot be reached by using laboratory tests, neuroimaging, or other technological tools. Instead of technological methods, the diagnosis of depression is reached by listening to the patient's report, by observations made by the clinician, and in some cases additive information is gathered from reports from those close to the patient. Diagnostic criteria consist of a cluster of typically simultaneously presenting symptoms forming a clinical entity. (Table 1.) As symptoms of depressions differ from each other, sometimes presenting with even opposite ends of the spectrum such as lack of appetite vs. overeating, subdivisions of the diagnosis have been suggested. Atypical depression (Quitkin, 2002), postpartum depression (Henshaw, 2003), and vascular depression (Alexopoulos et al., 1997), are clinically defined, commonly accepted subtypes of depression. Despite other efforts trying to subclassify depression, data-driven classification fails to identify meaningful subgroups (van Loo et al., 2012).

Table 1.Definition of Major depressive disorder according to DSM-IV and ICD-10 criteria.

	DSM-IV	ICD-10
Clinical significance	Significant stress or impairment in social, occupational or other important areas of functioning	Some difficulty with work and social activities, considerable difficulty in moderate episode, considerable distress or agitation and unlikely to continue functioning in severe episode
Duration of symptoms	Most of the day, nearly every day for at least two weeks	A duration of at least two weeks usually required
Symptoms and severity	Five or more of following symptoms; at least one symptom is depressed mood or loss of interest or pleasure	Depressed mood, loss of interest and enjoyment, and reduced energy leading to increased fatiguability
	Depressed mood	Reduced concentration and attention
	Loss of interest or pleasure	Reduced self-esteem and self-confidence
	Significant weight loss or gain or increase or decrease in appetite	Ideas of guilt and unworthiness
	Insomnia or hypersomnia	Bleak and pessimistic views of the future
	Psychomotor agitation or retardation	Ideas or acts of self-harm or suicide
	Fatigue or loss of energy	Disturbed sleep
	Feeling of worthlessness or excessive or inappropriate guilt	Diminished appetite
	Diminished ability to think or concentrate or indecisiveness	
	Recurrent thoughts of death, recurrent suicidal ideation without specific plan or suicide attempt or a specific plan	

The diagnosis of depression is based on the recognition of a typical cluster of symptoms. Simple screening instruments such as DEPS for primary care have been developed for the purpose (Salokangas et al., 1994). Although not originally designed for screening, the Beck Depression Inventory (BDI) (Beck and Steer, 2000) also is typically currently used for symptom identification. The current diagnosis of depression in most parts of the

world is based on commonly agreed criteria accepted by international communities of psychiatrists (DSM-IV, DSM-V and ICD-10 criteria (Table 1.). Some symptoms, such as depressed mood, are compulsory for the diagnosis, whereas others, such as the loss of appetite, are optional.

2.1.2 Prevalence and cost

According to the World Health Organization (WHO), depression globally affects 350 million people. It is the leading cause of disability worldwide. Suicide, highly associated with depression, is the second leading cause of death in 15–29-year-olds (Kessler et al., 1999). In Finland, the yearly prevalence of depression among adults is 5% (Pirkola et al., 2005). Women suffer from depression 1.5 to two times as often as men do. The prevalence in 2011 for women was 12.2% and for men 6.7% (Markkula et al., 2015). Roughly, 10% of all patients in primary health care and 50% of psychiatric patients in Finland are clinically depressed (Vuorilehto et al., 2005). In 2010 new permanent working disability pensions were granted to 4100 persons in Finland (Honkonen and Gould, 2011).

2.1.3 Differential diagnosis

Unipolar depression must be differentiated from bipolar disorder; in the latter, the mood of the patient alternates in cycles between states of elevation (hypomania and mania) and depression. Possible somatic causes of depressive symptoms, such as thyroid dysfunction, vitamin insufficiencies, malign tumours, and neurological (such as dementia), cardiovascular and endocrinological diseases, must be ruled out as well. Depressive symptoms may stem from substance abuse or dependency. Grief following the loss of a loved one has been differentiated from depression in diagnostic manuals as ICD-10 (World Health Organisation, 1992) and DSM-IV (American Psychiatric Association, 2000). However, in the the most recent diagnostic manual (DSM-V), this separation of grief and depression no more exists (American Psychiatric Association, 2013).

2.1.4 Comorbidity

Most patients suffering from depression have other comorbid syndromes. Commonly co-existing anxiety disorders include panic disorder and social phobia. Approximately half of treatment-seeking depression patients have a personality disorder (PD) with avoidant, borderline, and obsessive-compulsive PD as the most common forms (Fava et al., 1994; Fava et al., 2002). In a Finnish occupational health care sample, obsessive-compulsive PD co-occurred in 50% men and 28% women seeking treatment for depression (Raiskila et al., 2013). Substance use disorder is diagnosed in 10–30% of patients with depression (Melartin et al., 2002).

2.1.5 Psychological conceptualization

Several psychological models address the nature and etiology of depression. Different theoretical backgrounds and formalizations emphasize different dimensions and etiological factors of depression. A thorough review of all known models would be beyond the scope of the current thesis. Some of the most influential concepts are, however, briefly described here.

According to the psychoanalytical model, depression is related to a loss of a significant object. Different from common grief, in depression, the object is seen as an internalized part of the depressed person (Freud, 1917), and the negative feelings towards this lost important object are turned against the self of the person being depressed. Freud later

modified this theory, underlining the self-critical role of the psychological structure called super-ego, which corresponds to conscience. The term anaclitic depression refers to a form of depression occurring in the disruption of care received from a close one. This form of depression is typical in abandoned children. Introjective depression is a term used when the individual is unable to meet one's own demands or the ones perceived to be presented by others.

In the cognitive model of Beck (1979) negative automatic thinking, negative ways of perceiving self, the environment and the future, as well as maladaptive information processing, are associated with depression. This model distinguishes between original causes and maintaining causes of depression.

Behavioral theories include models of learned helplessness (Miller and Seligman, 1975) and neurotic maladaptive anxiety associated with negative feedback and inhibition of positive behavior (Wolpe, 1979).

The behavioral shutdown model (BSM) presents the negative emotions of depression as fulfilling functions similar to what pain does in physical illnesses. These negative emotions such as fear, anxiety, shame, or guilt, guide individuals in social situations. Depression is an inhibited strategy of survival in a frame of emotional investment and expected gain. The model unites biological explanations such as genetics, nurture, and environmental stress factors (Henriques, 2011).

2.1.6 Functional aspects of depression

It is puzzling that such a disabling and agonizing condition as depression is so widely experienced by the human population. It has been postulated that depression is an evolutionary adaptation to reduce risky behavior or social exclusion. Symptoms of depression may also call for concrete help from others or aid in the analysis of complex problems. Depression has also been viewed as a side-effect of an immunologic defense mechanism against pathogens or as a dysfunction of otherwise adaptive mood mechanisms. Given the variation in the different conditions under the label of depression, multiple evolutionary explanations exist (Kleppestø, 2018). Since depression, at least in the short term, is not associated with increased fitness or chances of reproduction, and since it is not sufficiently directly heritable, it may be viewed more as an adaptative than an evolutionary phenomenon (Sharpley & Bitsika, 2010).

2.1.7 Biological etiology

Biological views of depression comprise multiple findings and theories connected with functional alterations of various neurotransmitter systems such as serotonin and catecholamines, as well as immunological and neuroendocrinological mechanisms (Kupfer et al., 2012). Dysregulation of the hypothalamic-pituitary-adrenocortical system (HPA-axis) has been established as one commonly found feature of MDD (Holsboer, 2000). The estimate of the heritability of MDD in meta-analysis of twin studies is 32% (Sullivan et al., 2000) and meta-analysis of genetic similarity among individuals with MDD reports heritability of 37% (Lubke et al., 2012).

2.2 SEROTONIN SYSTEM IN DEPRESSION

2.2.1 Pharmacological shots in the dark

Revolutionary medical findings in the 1950s are considered the starting point of biological psychiatry. The tuberculosis medicine, iproniazid, was found to alleviate symptoms of depression (Udenfriend et al., 1957a). At the same time, an antihypertensive

agent, reserpine, was found to cause symptoms of depression (Pletscher et al., 1955; Brodie et al., 1957; Davies and Shepherd, 1955). Furthermore, in early trials to treat patients with schizophrenia, imipramine failed to reduce symptoms of psychosis but lifted the mood in some patients (Kuhn, 1957). Imipramine also antagonized some of the depressogenic effects of reserpine. These findings were followed by a search of the mechanisms involved. The tuberculosis medicine, iproniazid, inhibited monoamine oxidase; reserpine depleted noradrenaline in nerve endings; and imipramine blocked noradrenaline reuptake. Taken together these, at first serendipitious, findings, with the analysis that followed them, led to the development of the cathecholamine theory of depression (López-Muñoz and Alamo, 2009).

2.2.2 Serotonin

An endogenous compound causing the constriction of small blood vessel walls was found in gastrointestinal enterochromaffin cells. It was first named enteramin and later serotonin (5-HT) (Erspamer and Asero, 1952). Soon, it was found to act as a neurotransmitter as well (Gaddum, 1953). (Figure 1)

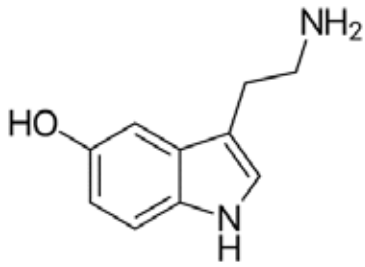

Figure 1. Molecular structure of serotonin. Adapted from National Center for Biotechnology Information.[1]

[1] PubChem Compound Database. https://pubchem.ncbi.nlm.nih.gov/#query=serotonin

2.2.3 Monoamine theory of depression

Pharmacological findings of the role of monoamines in depression led to two main theories: one emphasizing noradrenaline (Schildkraut, 1965) and another underlining serotonin (Coppen, 1967).

Initially, the role of noradrenalin in depression pathogenesis was thought to be more important, but the finding of the antidepressive effects of 5-hydroxytryptophan, the precursor of serotonin, shifted the attention to serotonin (Persson and Roos, 1967; Udenfriend et al., 1957b). The role of tryptophan and serotonin has been further underlined by studies reporting lower concentrations of free tryptophan in the plasma of depressed patients (Quintana, 1992) and the relapse of symptoms of depression with induced depletion of tryptophan (Delgado et al., 1990).

The first proof of tricyclic antidepressants (TCAs) blocking serotonin reuptake in the brain was found by a research team led by Arwid Carlsson (1968); at the time, TCAs were commonly used. A widely cited review stated that all antidepressants recognized at that time, as well as electroconvulsive therapy (ECT), increased synaptic serotonin levels (Lapin and Oxenkrug, 1969). However, a typical two- to four-week delay exists in the action of serotonergic drugs. This delay was explained by findings that TCAs and ECT improve the efficiency of serotonergic transmission mediated by the downregulation of presynaptic 5HT1A autoreceptors. Blocking 5-HT reuptake increases the level of synaptic 5-HT and, in two to four weeks, downregulates 5-HT1A, causing disinhibition and increased firing of the presynaptic neuron. 5HT1A autoreceptors are also found in the postsynaptic serotonergic cells of the limbic system and cortex, and the regional influence of antidepressants may be of importance (Hjorth et al., 2000; Blier and Ward, 2003).

It is not yet possible to measure 5-HT or its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the living human brain, but postmortem studies of depressed patients have found decreased 5-HT and 5-HIAA concentrations in the cerebrospinal fluid (CSF), whole brain, amygdala and hypothalamus. In living subjects, however, jugular venous 5-HIAA concentration, which was considered a marker of 5-HT turnover, was elevated in depression; this elevation was most evident in patients with a low SERT-expressing genotype. Treatment with SSRI reduced the jugular 5-HIAA level to that of healthy controls (Barton et al., 2008).

Based mainly on animal models of depression, it has been proposed that serotonin levels are actually increased in depression and that the delayed effect of antidepressants is due to the efforts of the central nervous system (CNS) to re-establish energy homeostasis (Andrews et al., 2015).

2.2.4 Serotonergic network

Nearly all areas of the CNS have functions mediated by the serotonin system (Figure 2.). The somas of approximately 350 000 serotonin neurons are located in the midbrain raphe nuclei, from which axons originate in two main bundles. The rostral part of sertonergic dendrites projects to the cortex and limbic system; the caudal part is connected to the medulla and spinal cord. Serotonin modulates multiple functions of the CNS, including the regulation of mood, cognitive functions, anxiety, appetite, sexual drive, thermoregulation, and pain perception. Serotonin seems to modulate almost all the functions of the CNS (Charnay and Léger, 2010); at the same time, on its own, it is responsible for none (Muller & Homberg, 2015). Multiple sites of action and numerous receptors (Hoyer et al., 1994) have prompted researchers to call the 5-HT system elusive and "a puzzle" (Dayan and Huys, 2009).

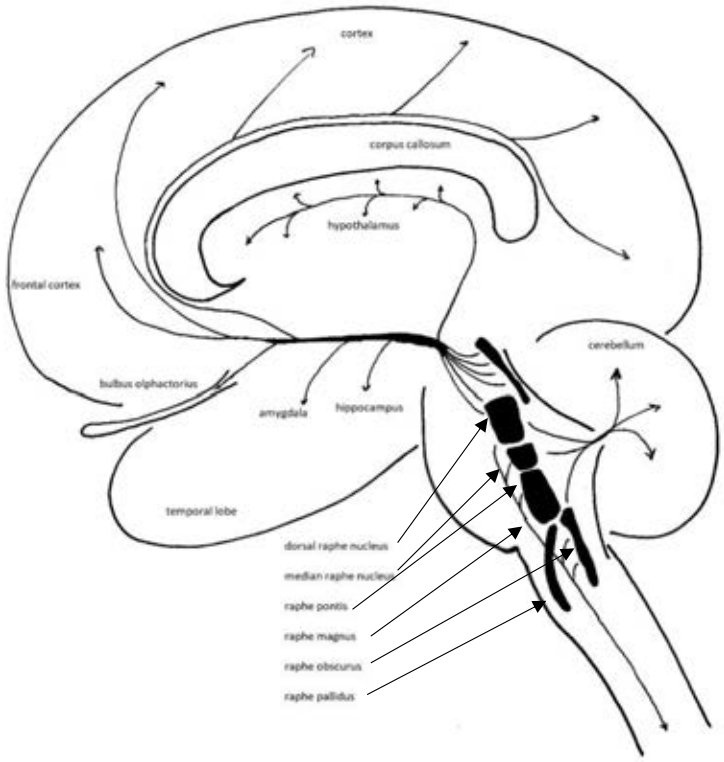

Figure 2. Schematic map of serotonin network in the human brain. The raphe nuclei of the serotonergic system are situated in the brain stem, a part of which is also referred to as the midbrain area.[2]

2.2.5 Serotonin and stress

Several findings in animal studies point toward increased serotonergic activity in the presence of stress (Adell et al., 1997; Fujino et al., 2002; Funada and Hara, 2001; Maswood et al., 1998; Rueter et al., 1997).

Proper functioning of the 5-HT system is necessary for adaptive responses of an organism against aversive events. Based mainly on animal studies, at least three mechanisms of disruption of this system have been suggested: imbalance of 5HT2 and 5HT1 receptors, hypercortisolemia during chronic stress, and social isolation (Deakin & Graeff, 1991).

According to a two-receptor model, the moderation of stress and increased patience is mediated by 5-HT1A, and open-mindedness is mediated by 5-HT2A (Carhart-Harris & Nutt, 2017).

Following complex indirect findings from human neuroimaging and genetics, it has been postulated that chronic stress may cause elevated 5-HT levels. This elevation, in turn, is followed by the downregulation of serotonin receptors, causing a vicious circle; because of fewer receptors, 5-HT has decreased response. This decreased effect of 5-HT

[2]Adapted from Nieuwenhuis R. Monoamines: Chemoarchitecture of the Brain. Berlin, Germany: Springer Verlag; 1985:33-41.

is called serotonin resistance and resembles insulin resistance in type two diabetes (Smolin et al., 2007).

Adolescent social isolation decreases the expression of tryptophan hydroxylase 2 in rat adulthood. This aspect can be interpreted as indirect evidence for the environmental long-lasting modulation of the serotonergic system (Lukkes et al., 2013).

2.3 SERT

The serotonin transporter (SERT) is the primary target of widely used antidepressants such as fluoxetine, paroxetine, citalopram, and sertraline (Owens and Nemeroff, 1994; Eshleman et al., 1999; Murphy DL et al., 2004). Furthermore, illicit drugs, such as amphetamine derivatives fenfluramine, p-chloroamphetamine (PCA), and 3,4 – methylenedioxymethampetamine (MDMA or "Ecstasy"), all of which are associated with elevated mood, bind to SERT (Rudnick & Wall, 1992).

Neurotransmitter transporters are plasma membrane proteins responsible for the reuptake of neurotransmitters from the synapse. Neurotransmitter transporters terminate the action of the transmitter; at the same time, they initiate the recycling of the transmitter for subsequent firing (Blakely, 1994; Rudnick, 2006; Torres & Amara, 2007).

Multiple areas of the human body contain SERTs (Lesch et al., 1993). They are found in the lymphocytes of the intestine (Gordon and Barnes, 2003), placenta (Balkovetz et al., 1989), lung (Paczkowski et al., 1996), adrenal chromaffin cells (Schroeter et al., 1997), blood lymphocytes (Faraj et al., 1994), and blood platelets (Carneiro & Blakely, 2006; Carneiro et al., 2008).

2.3.1 Structure of the SERT

The SERT was identified and cloned in the rat brain (Blakely et al., 1991) and human brain (Ramamoorthy et al., 1993) and characterized with antibodies. Most small neurotransmitters are transported by proteins belonging to the neurotransmitter sodium symporter (NSS) family (Dahl et al., 2004). The SERT is a transmembrane protein situated on the cell surface. The three-dimensional structure of the SERT is not yet accurately known. It is, however, predicted to have 12 transmembrane domains.

2.3.2 Function of the SERT

The SERT selectively transports 5-HT into nerve cells together with Na^+ and Cl^- while simultaneously transporting a K^+ ion out of the cell. (Rudnick, 2006). The SERT and 5-HT concentrations correlate in several areas of the rat brain and rabbit brain (Dewar et al., 1991) (Figure 3).

2.3.3 SERT and 5-HT challenges

SERT availability is only an indirect marker of endogenous 5-HT transmission. Although direct measurements of endogenous 5-HT are now possible only in animal studies, a few 5-HT challenge studies have addressed this question. In tranylcypromine challenges, the inhibition of monoamine oxidase and the following increase of 5-HT is associated with decreased SERT availability in animals (Ginovart et al., 2003; Lundquist et al., 2005; Lundquist et al., 2007). Similar changes surfaced in one study combining the 5-HTP challenge, microdialysis, and PET imaging. Increased regional 5-HT accompanied a decrease of SERT binding in the same brain regions (Yamamoto et al., 2007). Three PET studies with tryptophan depletion have yielded mixed results, with a paradoxical reduction in SERT availability in baboons (Milak et al., 2005) and no change in healthy humans (Praschak-Rieder et al., 2005; Talbot et al., 2005). Taken together, challenges with

an increase of 5-HT were associated with decreased SERT availability while challenges with a decrease of 5-HT yielded either decrease or no change in SERT availability.

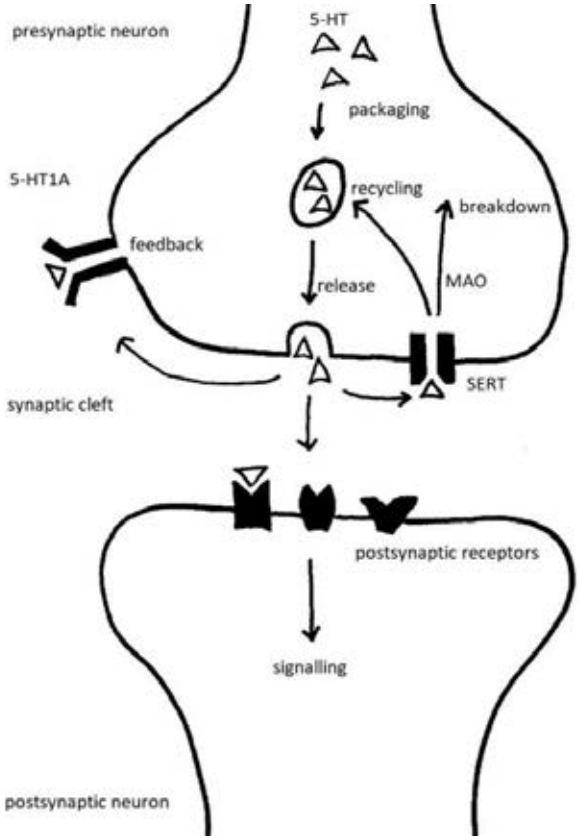

Figure 3. Synaptic function of the SERT: Trytophan is converted to serotonin, packaged into vesicles, and released into the synaptic cleft. Presynaptic autoreceptors 5-HT1a give feedback to the presynaptic neuron. Postsynaptic 5-HT receptors transmit signals to the postsynaptic neuron. The serotonin transporter SERT moves 5-HT back to the presynaptic cell, where it can be oxidized or recycled.[3]

[3]Adaptation from aan het Rot et al., 2009

2.3.4 Distribution of the SERT

The serotonin system is widespread in the human brain. The dorsal and median raphe nuclei are situated in the midbrain pons and connected with multiple cortical and subcortical structures (Beliveau et al., 2017; Pollak Dorocic et al., 2014) (Figure 4). According to a recent multimodal connectivity study, both these raphe nuclei are functionally connected with the anterior cingulate, amygdala, insula, hippocampus, thalamus, basal ganglia, and cerebellum (Beliveau et al., 2015).

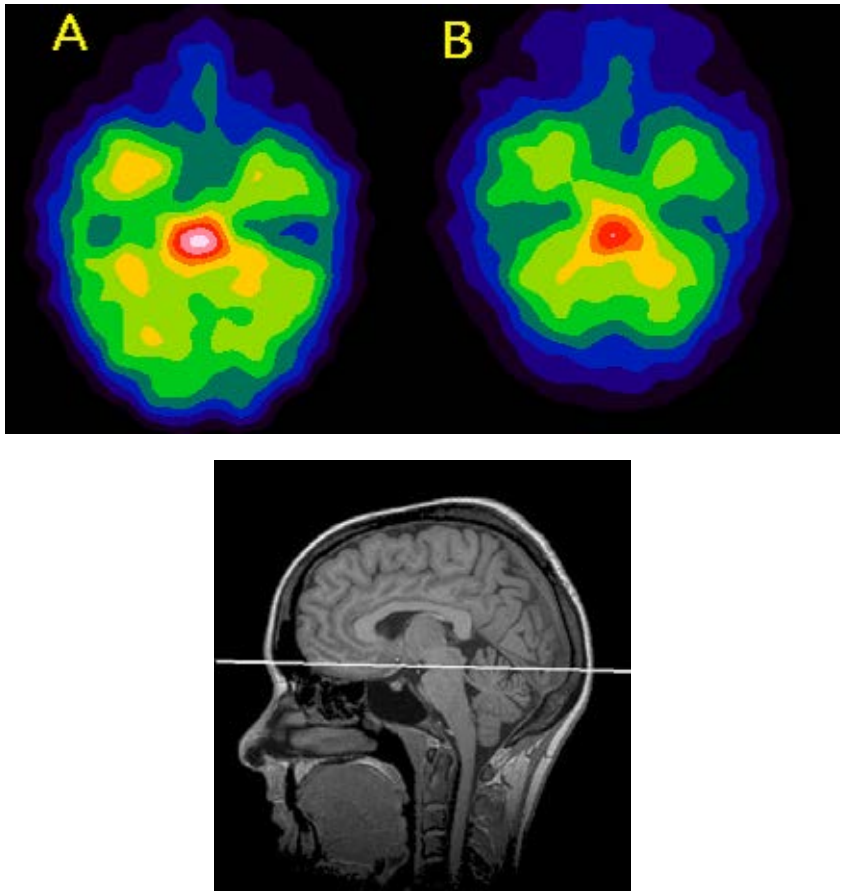

Figure 4.An example of [123I] nor-β-CIT SPECT imaging of the midbrain Kuopio University Hospital Department of Clinical Neurophysiology. A: Healthy control subject, B: patient with MDD. In the sagittal T1-weighted anatomical MRI scan, the white line indicates the plane of midbrain imaging cutting through dorsal and median raphe nuclei.

2.3.5 Genetics of the SERT

SERT expression is regulated by a common polymorphism of a promoter gene upstream of the protein coding region. Two main variants of the promoter exist: long (L) and short (S), with one copy inherited from either parent producing LL-, LS- and SS-genotypes (Heils et al., 1995). The long variant further has a single nucleotide polymorphism (SNP), and the allele is divided into two subtypes, La and Lg (Nakamura et al., 2000). In cell

culture, the La genotype produces more of the SERT. The balance of genotypes differs geographically and ethnically, with more S-genotypes in eastern Asia and more L-genotypes in Northern America (Eisenberg and Hayes, 2011).

In populations with European ancestry, the distribution of the alleles is: LL 0.36, LS 0.48, SS 0.16 (Gelernter et al., 1997). In a Finnish population sample, the distribution of allelic combinations was: SS 0.15, SLa 0.44, SLg 0.08, LaLa 0.24, LaLg 0.09, LgLg 0.01. In the same sample, the allelic distribution was: S 0.40, La 0.51, Lg 0.09 (Hu et al., 2006).

Several converging lines of evidence from 5-HTTLPR studies point towards the role of the SERT in depression. According to the famous Dunedin cohort study, the S-genotype is associated with vulnerability to depression in the context of adverse life events (Caspi et al., 2003). This interesting finding connecting genetic predisposition and environmental factors inspired several replication studies, which yielded mixed results. One meta-analysis seemed to confirm the original results (Karg et al., 2011); the most recent and largest (38 802 subjects) meta-analysis (Culverhouse et al., 2018), however, fails to support the association of the S-allele and vulnerability to depression under stress.

Pharmacogenetic studies have associated better treatment response with the L-allele (Serretti et al., 2007) and increased side effects with the S-allele (Murphy GM et al., 2004).

Along with 5-HTTLPR, another polymorphism within intron 2 of the SERT gene consists of a variable number of tandem repeats (VNTR). It contains 9, 10, or 12, copies of an element of 17 base-pairs. The 12-copy variant has been associated with bipolar disorder but not with unipolar depression (Collier et al., 1996).

2.3.6 Epigenetics of the SERT

Environmental and developmental factors influence the expression of genes. Altered methylation of DNA coding the SERT has been reported in association with traumatic life events (Beach et al., 2011; Philibert et al., 2008); this SERT methylation change is related to psychotherapy response in children with anxiety disorders (Roberts et al., 2014). Furthermore, the methylation of the SERT DNA related to gray matter volume of the hippocampus in healthy subjects (Dannlowski et al., 2014).

In addition to the methylation of 5-HTTLPR itself, it seems that another source of variation in SERT expression is an island situated 1000 base pairs downstream of 5-HTTLPR. Variation in this CpG island is associated with SERT mRNA levels (Philibert et al., 2007).

In elderly individuals homozygous for the S-allele, low methylation in two CpG sites was associated with depression (Lam et al., 2018).

Micro RNAs are small, non-coding fragments of RNA involved in the posttranscriptional regulation of gene expression. Micro RNA-16 (Mir-16) is one of the epigenetic factors regulating SERT expression. Findings from both animal and human studies suggest that decreased levels of Mir-16 exist in the cerebrospinal fluid of depressed subjects and that neutralization of Mir-16 induces depression-like behavior in rats (Song et al., 2015). Chronic treatment with fluoxetine increases MiR-16 levels which, in turn, reduces SERT expression in mice (Baudry et al., 2010).

2.3.7 Emotional processing and the SERT

Evidence of the role of the SERT in emotional processing began to accumulate after the finding of the 5-HTTLPR effect on neuroticism (Lesch et al., 1993). This association of SERT and neuroticism is further supported by a more recent, large in vivo PET study suggesting different correlation in women and men. In women higher neuroticism was associated with lower SERT availability whereas the opposite correlation was found in men (Tuominen et al., 2017). Pharmacological inhibition of the SERT seems to induce

positive perceptual bias, affecting the processing of both internal and external input of information (Harmer et al., 2004, Harmer and Cowen, 2013). In a mice animal model, SERT overexpression was associated with reduced negative bias in uncertain situations (McHugh et al., 2015). A review of the effect of the SERT on social cognition in both humans and other species points towards a broad effect connected with the brain mirror neuron system (Canli and Lesch, 2007). The high SERT-expressing L-allele is associated with a bias in processing visual information, selectively favoring positive and neglecting negative information (Fox et al., 2009). Evidence also exists for increased responsivity to both negative and positive emotions in social situations in individuals with the S-allele (Schoebi et al., 2012). However, subjects with high psychopathy scores have an exceptionally low incidence of depression (Cleckley, 1941). Low emotional reactivity, i.e. callousness, is associated with the high SERT-expressing 5-HTTLPR L-allele in combination with low socioeconomic status (Sadeh et al., 2010) and increased SERT availability in the anterior cingulate cortex (van de Giessen et al., 2014).

5-HTTLPR allelic variation correlates also with changes in brain structures associated with emotional processing. Decrease in the size of the hippocampus is a widely replicated MRI finding in depression (Videbech and Ravnkilde, 2004). The S-genotype relates to decrease of the hippocampal volume in depression and increased amygdala activity during processing of negative visual information (Hariri et al., 2002). The S-allele is also associated with decreased activity of the corticolimbic loops between the gyrus cingulate and amygdala (Pezawas et al., 2005). The 5-HTTLPR polymorphism also affects cortical thickness, and several studies report reduced grey matter volume for S-allele carriers in the anterior gyrus cingulum (Selvaraj et al., 2011). Recent findings, however, suggest a more complicated model. In a group with high familial risk of depression, the S-allele was associated with a thicker cortex; in the low risk group, the effect was the opposite (Bansal et al., 2016).

2.3.8 Positive aspects of lower SERT expression

Lower SERT expression is not associated only with vulnerability or negative aspects of human nature. On the contrary, the lower SERT-expressing S-allele is associated with numerous positive features, such as increased emotionality and cognitive abilities, in both animal and human studies (Homberg and Lesch, 2011). These advantageous associations may explain the perseverance of the S-allele in humans and other primates (Dobson and Brent, 2013). From a larger perspective, even sociocultural aspects may be interactively associated with the genotype distribution of 5-HTTLPR. This may indicate that vulnerability to depression modulated by 5-HTTPLR must be evaluated in the context of both culture (Chiao and Blizinsky, 2010) and individual adaptational challenges (Caspi et al., 2003; Karg et al., 2011).

2.3.9 Inflammation and the SERT

Inflammation is one important factor in the modulation of mood. Abundant evidence points towards an important role of inflammatory mechanisms in depression. This is, however, not in contradiction with other explanations, including the monoamine theory of depression. Recent findings connect physical and psychological stress, neurotransmitters, and inflammation (Miller and Raison, 2016). The SERT is affected by inflammation as its mRNA expression and transporter density are increased by both interleukin 1 β (IL-1β) (Ramamoorthy et al., 1995; Metaxas et al., 2018) and tumor necrosis factor (TNF) induction of p38 mitogen-activated protein kinase (MAPK). These changes decrease the synaptic availability of serotonin and depressive-like behavior in laboratory

animals. This feature suggests a pathway where stress can cause inflammation which, in turn, affects the monoamine system and causes despair-like behavior (Zhu et al., 2010).

2.3.10 Serotonin, the SERT, and neuroplasticity

To be able to learn and cope with changing environments, an organism needs to remember. Serotonin modulates the formation of memory (Kandel, 2012) and opens a window for plasticity (Maya Vetencourt et al., 2010). Although human studies are still only suggestive in nature, animal data clearly demonstrates the link 5-HT has with numerous growth factors and other cellular mechanisms connected with neuroplasticity. Examples are protein kinase B (AKT), brain-derived neurotrophic factor (BDNF), response element-binding protein (cAMP), extracellular signal-regulated kinases (ERKs), cellular level long-term depression (LTD), long-term potentiation (LTP), mitogen-activated protein kinases (MAPKs), N-methyl-d-aspartate receptor (NMDA), nuclear factor kappa light-chain-enhancer of activated B cells (NF-B), polysialylated neuronal cell adhesion molecule (PSA-NCAM), and tyrosine receptor kinase B (TrKB) (Kraus et al., 2017). Recent studies indicate that molecular changes are insufficient. In addition to changes in the serotonin system and the BDNF, activity is necessary. Molecular changes provide a window for adaptation; in the absence of activity, however, this possibility is missed (Castrén and Rantamäki, 2010). In addition, the effects of rearing (nurture) on serotonin associated plasticity are evident in animal models. In genetically modified rats with reduced SERT expression, maternal separation led to an overall reduction in BDNF expression in the ventral hippocampus and ventromedial PFC; however, in the dorsal hippocampus and dorsomedial prefrontal cortex (PFC), a significant increase in neurotrophin gene expression after maternal separation was observed. According to Calabrese et al., (2015) it seems possible that the SERT modifies sensitivity to change "for better and for worse". In cases where preceding stress matches subsequent environment, this may provide an adaptational advantage. SERT-environment interaction not only modifies vulnerability to anxiety or depression but is more broadly connected with adaptation and plasticity (Houwing et al., 2017).

2.3.11 HPA and the SERT

The stress-related hormonal function of the hypothalamus pituitary axis (HPA) has been strongly associated with depression. Recent evidence connects SERT function also with HPA function. Morning cortisol awakening response (CAR) levels correlate positively with prefrontal SERT availability (Froekjaer et al., 2013). In a dexamethasone-corticotropin test, higher SERT availability was associated with smaller percentual reduction in cortisol levels, following dexamethasone administration (Reimold et al., 2011; Tsai et al., 2012; Tsai et al., 2013). The 5-HTTLPR genotype had no effect on CAR (Frokjaer et al., 2013); in a Dex-CRH test, however, a weak interaction with smaller response in S-carriers emerged (Reimold et al., 2011). In the first human study combining HPA function 5HTTLPR and stressful life events in an elderly population, SS-homozygous individuals with elevated morning cortisol levels had a four-fold elevated risk of depression. In the same study, SL-heterozygotes were the most resilient against depression (Ancelin et al., 2017). Further evidence of the interaction of the SERT and HPA comes from animal studies, in which the contributing factors of nurture and nature are more controllable. The 5-HTTLPR genotype interacts with rearing conditions (maternal rearing vs. peer rearing), influencing cortisol and ACTH response during acute stress. Inadequately reared macaques with a lesser SERT-expressing genotype, after separation from their mothers, had a higher adrenocorticotropic hormone (ACTH) response (Barr et

al., 2004a). Further analysis, however, limited the interaction of the S-allele and maternal separation to females (Barr et al., 2004b).

2.3.12 Other factors affecting SERT availability

Aging is associated with an approximately 4.2% decrease per decade in SERT availability (van Dyck et al., 2000). In a recent meta-analysis, the mean age of study subjects was also associated with an increase in the difference between MDD patients and healthy controls. Adolescents exhibit elevated SERT availability in depression (Dahlström et al., 2000).

Findings regarding the effect of gender on SERT availability in depression are contradictory. While Staley et al. (2006) observed decreased SERT availability in depression only in women, Ruhe et al. (2009) found decreased SERT only in men.

Sex hormones influence SERT activity. In ovariectomized macaques, oestrogen increases SERT mRNA and SERT availability (Bethea et al., 2011). In males, lack of testosterone, often associated with depression, may contribute to decrease in SERT as testosterone is converted to oestrogen. In male rats, reduced SERT availability caused by aging is partially restored with testosterone restitution (Herrera-Pérez et al., 2013).

Studies of seasonal effects on SERT availability have yielded mixed findings. Winter decreased SERT availability in one study (Neumeister et al., 2000). Winter, however, increased SERT availability in three studies (Buchert et al., 2006; Praschak-Rieder et al., 2008; Ruhé et al., 2009). The effect of season on SERT availability may relate to the serotonergic activity of the suprachiasmatic nucleus (Ruhé et al., 2009). One study in Finland found no changes within healthy subjects in winter and summer SERT availability (Koskela et al., 2008a). Seasonally changing temperature correlates with a one-month delay with blood platelet SERT availability, which may correlate with brain SERT availability (Tiihonen et al., 2017).

Smoking could be a confounding factor in SERT neuroimaging studies. At least two studies on the subject exist. In one on men, higher brainstem SERT availability was associated with smoking (Staley et al., 2001). In another, smoking male MDD patients had significantly lower SERT availability in the diencephalon than smoking male controls did; non-smoking female patients had higher SERT availability than non-smoking female controls did (Ruhe et al., 2009). A recent PET study in healthy males, however, found no effect of smoking on SERT availability (Zhao et al., 2016).

A diagnosis of alcoholism and lifetime intake of alchohol are associated with reduced availability of brainstem SERT (Heinz et al., 1998). Reductions in SERT availability are limited to homozygous carriers of the 5HTTLPR long allele and correlated with negative mood states (Heinz et al., 2004). In a study of the Finnish population, S-allele frequency was associated with an increased risk of early onset alcoholism associated with antisocial personality disorder and impulsive, habitually violent behavior (Hallikainen et al., 1999). In mice, alcohol, by inhibiting SERT function, inhibits the clearance of serotonin in the hippocampus (Daws et al., 2006).

In a twin study, higher body weight was associated with higher SERT availability (Koskela et al., 2008b). Another study found non-obese subjects had a positive correlation of weight with the SERT; for obese subjects, the correlation was negative (Nam et al., 2018).

Anxiety disorders are typical comorbidities of depression, and symptoms in rating scales of depression include anxiety. Panic disorder studies have reported both decrease (Maron et al., 2004) and increase (Maron et al., 2011) of SERT availability. SERT availability between patients with generalized anxiety disorder (GAD) and healthy controls was similar (Lee et al., 2015).

In a fairly large sample of healthy subjects, perceived amount of social support was recently found to correlate with SERT availability (Huang et al., 2013). In a pilot study, a

negative social environment affected SERT availability. Depressed subjects with a history of childhood abuse had lower SERT availability than non-abused subjects with MDD did, across all brain regions (Miller et al., 2009). Even the early phase of romantic love decreases blood platelet SERT binding (Marazziti et al., 1999).

2.4 IMAGING STUDIES OF THE SERT IN DEPRESSION

2.4.1 Platelet studies

The SERT is expressed in blood platelets, where it has a role in the vasoconstriction. Decreased SERT binding in blood platelets was found in depression (Meltzer et al., 1981). In the 1980s and 1990s, most blood platelet binding studies on depressed patients reported a significant state-dependent decrease of [3H]-imipramine binding (Langer and Galzin, 1988).
In healthy human subjects, the SERT activity of blood platelets has been associated with the function of the default mode network (DMN) (Scharinger et al., 2014). The DMN is one of the connectivity networks identified in the human brain. Its overactivation has been associated with depression (Zeng et al., 2012) and, more specifically, depressive rumination (Hamilton et al., 2015).

2.4.2 Postmortem autoradiography

Findings of SERT availability in MDD in postmortem autoradiography studies are inconsistent. Most postmortem audiographical studies are performed on the brains of victims of suicide. Suicide is strongly connected with depression, but also confounded by factors of poor impulse control and violence, both also known to be associated with serotonin. In a recent meta-analysis of postmortem studies of SERT availability, it was reduced in the amygdala and hippocampus, but not in the pons including the midbrain (Kambeitz and Howes, 2015).

2.4.3 Structural neuroimaging and SERT

An established finding in MDD, the decrease of the hippocampal volume (McKinnon et al., 2009), is associated with interactions of 5-HTTLPR with both childhood adversity and poor parenting (Frodl et al., 2010; Little et al., 2015). This finding is further supported by the association of stress-related 5HTTLPR methylation and reduced volume of the hippocampus (Booij et al., 2015).

2.4.4 In vivo SERT neuroimaging

SPECT imaging is based on the detection of gamma rays emitted by radioactive substances that are brought typically intravenously into the human body (Figure 5). In some imaging protocols, radioactive compounds are attached to molecules that stay in the blood stream, making it possible to visualize blood flow. Other combinations of radioactive substance and molecules, also called radiopharmaceuticals or ligands, target glucose metabolism or desired molecules, such as receptors and transport proteins. High energy photons (gamma rays) are recorded with gamma cameras from various angles, and computerized calculations produce estimated images of the distribution of ligands. In these estimations, scatter, attenuation, and depth blurring, must be corrected with various models. Typically, the resolution of SPECT imaging of the human brain is 8–12 millimeters (Khalil et al., 2011). Another method of nuclear imaging is positron emission tomography (PET). It is based on the detection of simultaneously emitted photons in

opposite directions. The spatial resolution of PET is 4–6 mm, making it more accurate than SPECT in the anatomical localization of signals (Khalil et al., 2011). An important aspect of nuclear molecular imaging is the specificity of the binding of the ligand (Wernic and Aarsvold, 2004). SPECT and PET are able to produce acceptable images at a relatively low rate in the field of view. In SPECT the temporal resolution is some minutes whereas in PET the image acquisition rate is few seconds.

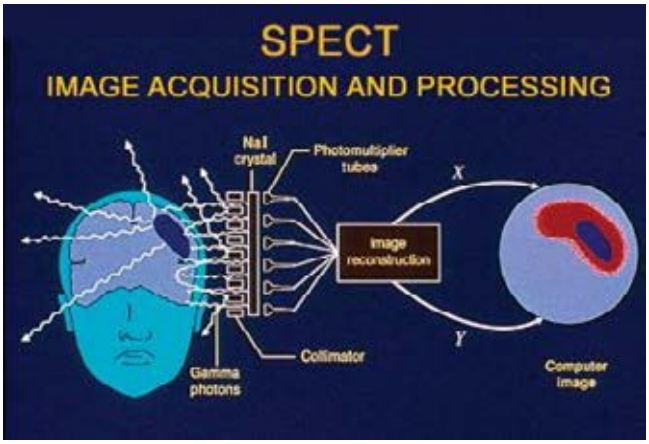

Figure 5. Schematic diagram of the method of SPECT imaging.Gamma photons emmited by the radioactive ligand travel through the collimator and are then converted into electrical activity. Reconstruction algorithms produce the final images. [4] (De Deyn et al, 1997)

Neuroimaging of the SERT in living human subjecs became possible in 1991, with the development of single photon emission computed tomography (SPECT) with radioligand [123I] β-CIT and, a few years later, the more SERT-selective [123I] nor-β-CIT (Innis et al., 1991; Bergström et al., 1997; Hiltunen et al., 1998). These compounds, however, also bind to dopamine (DAT) (Laruelle et al., 1993) and noradrenaline transporters (NORTs). This feature has led studies using these ligands to concentrate on SERT-dense regions, such as the midbrain. Ligands compete with endogenous serotonin at SERT-binding sites (Heinz et al., 2004b). Another SERT selective ligand [123I]ADAM has been used in several clinical studies. (Oya et al., 2000). Further development has led to the use of selective positron emission tomography (PET) radioligands [11C] (+)McN5652, [11C]DASB, [123I]ADAM and [11C] MADAM (Acton et al., 2001; Frokjaer et al., 2008; Halldin et al., 2005). The development, different techniques, and cautions regarding the interpretation of SPECT and PET neuroimaging of SERT are extensively reviewed by Brust et al. (2006).

SPECT and PET studie of MDD have yielded mixed results (Table 2). According to a recent meta-analysis of 18 PET and SPECT studies covering 364 MDD patients, SERT availability in the midbrain and amygdala of unmedicated depressed patients is reduced by approximately 10%, compared with healthy controls, with an effect size of 0.49 (Gryglewski et al., 2014). For comparison, a similar magnitude of effect size emerged in the increase in the utilization of DOPA decarboxylase substrates in a meta-analysis of

[4] Adapted with permission from Elsevier from: Masdeu, J.C. 2007. 76 - Single-Photon Emission Computed Tomography. In Gilman, S. (ed.) Neurobiology of Disease. Academic Press, 829-837.

schizophrenia (Howes et al., 2012). Another meta-analysis had 877 subjects with depression and obseved similar results in studies with living subjects; postmortem studies, however, revealed no decrease of SERT binding in the midbrain area (Kambeitz and Howes, 2015).

Although genes seem to affect vulnerability to depression, efforts aiming at pinpointing the effect of heritability on the central nervous system (CNS) in humans have produced mixed results.

In subjects with a first-degree family history of MDD, SERT availability in the midbrain was significantly lower than in healthy subjects without a family history of MDD (Hsieh et al., 2014). Healthy twin siblings of depressed subjects had decreased SERT availability in the dorsolateral prefrontal cortex (Froekjaer et al., 2009). Two PET studies, one with both healthy and depressed subjects (Parsey et al., 2006) and one with only healthy subjects (Shioe et al., 2003), however, found no 5HTTLPR-associated differences in the SERT. In one study with alcoholics subjects homozygous for the La had higher SERT availability in the putamen (Heinz et al., 2000). This association was stronger in another study when subjects from other than Caucasian origin were excluded (Praschak -Rieder et al., 2007) One study combined the assessment of amygdala reactivity, 5HTTLPR genotype and SERT availability of patients with MDD. High SERT availability in raphe nucleus predicted lower right amygdala reactivity to shown angry or fearful facial expressions. 5HTTLPR, however, did not affect amygdala reactivity. (Schneck et al., 2016).

Table 2. In vivo SERT neuroimaging studies of patients with MDD vs. healthy controls

1. Author	year	modality	ligand	n MDD/hc	main findings
Malison	1998	SPECT	[123I] β-CIT	15/15	decrease in brainstem
Newberg	2005	SPECT	[123I]ADAM	7/6	decrease in midbrain, correlation of symptoms and binding
Catafau	2006	SPECT	[123I]ADAM	10/10	no difference
Herold	2006	SPECT	[123I]ADAM	21/13	no difference
Staley	2006	SPECT	[123I] β-CIT	32/32	decrease in women in lower diencephalon
Joensuu	2007	SPECT	[123I]-norβ-CIT	29/19	decrease in midbrain
Ruhé	2009	SPECT	[123I] β-CIT	45/48	decrease in men in midbrain
Newberg	2012	SPECT	[123I]ADAM	20/10	decrease in midbrain, temporal lobes and basal ganglia
Ho	2013	SPECT	[123I]ADAM	40/12	decrease in thalamus
Ichimiya	2002	PET	[11C]McN5652	7/21	increase in thalamus, no difference in midbrain
Meyer	2004	PET	[11C]DASB	20/20	no difference in any brain region
Reivich	2004	PET	[11C]McN5652	4/4	increase in left frontal and right cingular cortex
Parsey	2006	PET	[11C]McN5652	12/43	decrease in amygdala and midbrain, (drug-naïve lower than drug-free)
Cannon	2007	PET	[11C]DASB	18/34	increase in thalamus, insula, striatum, periaqueductal gray
Reimold	2008	PET	[11C]DASB	10/20	reduced in thalamus, correlation with anxiety
Selvaraj	2011	PET	[11C]DASB	12/24	reduced brain stem, thalamus, caudate, putamen, anterior cingulate cortex and frontal cortex
Miller	2013	PET	[11C]DASB	51/31	no difference in any brain region, suicidal patients with MDD reduced in midbrain vs. hc and non-suicidal MDD
Nye	2013	PET	[11C]ZIENT	11/10	decrease in midbrain/pons and putamen (MDD with suicide attempt)

2.5 TREATMENT OF DEPRESSION

2.5.1 Pharmacological treatment

Drug treatment is recommended in moderate or severe forms of depression. In 2012 in Finland, 444 184 people were taking antidepressants. In Finland in 2016, antidepressants were used by 476 174 patients, of whom 207 991 were using SSRIs (FIMEA, 2017). These drugs most frequently belong to the classes of selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), noradrenaline reuptake inhibitors (NARIs), and the older generation of tricyclic drugs. Drugs of other classes, such as monoamine oxidase inhibitors (MAOIs), quetiapine, and agomelatine, also are in use. Blocking the function of the SERT is the target of the most common group of antidepressants, the SSRIs. In 2016, antidepressant use in Finland was 87.82 defined daily doses (DDDs)/1000 inhabitants, of which SSRIs accounted for 38.63. The effect size for typically used antidepressants is 0.30, corresponding to that of treatments for some somatic chronic illnesses, such as hypertension, asthma, and diabetes (Gibertini et al., 2012; Khan et al., 2015). In a Cochrane review, SSRIs were more effective than placebo RR = 1.28, 95% SD 1.15–1.43, number needed to treat (NNT) median = 7. Treatment discontinuation because of side-effects was more common than for placebo number needed to harm (NNH) = 20–90 (Arroll et al., 2009). Subanaesthetic ketamine treatment rapidly alleviates the symptoms of depression (Aan Het Rot, 2012).

2.5.2 Other biological treatments

In severe cases of treatment-resistant depression, electroconvulsive therapy (ECT) is an effective treatment option (UK ECT Review Group, 2003). In a recent study, the effects of laughing gas (N2O) were connected to the slow wave pattern in posttreatment electroencephalography (EEG) (Kohtala et al., 2018). The study proposed a similar mode of action for several acutely excitatory treatment modalities. Transcranial magnetic stimulation (TMS) and repeated TMS (rTMS) are novel and recently widely studied treatment methods for depression (Perera et al., 2016). In the treatment of depression, vagal nerve stimulation (VNS) (O´Reardon et al., 2006) and deep brain stimulation (DBS) (Delaloye and Holtzheimer, 2014) are neuromodulation methods. The treatment of depression also employs physical exercise (Hearing et al., 2016), light therapy (Mårtensson et al., 2015), and sleep deprivation (Dallaspezia and Benedetti, 2015).

2.5.3 Psychotherapies

The treatment of depression involves multiple modalities of psychotherapy. Common factors of the most forms of psychotherapy include verbalization of emotions, thoughts, and memories. Psychotherapy includes social support and human interaction. In addition to individual psychotherapy methods, pair, family, and group, therapies are available. Comparative research of the efficacy of different therapies has been contradictory. The personality of the therapist, quality of the working alliance, and patient-therapist interaction, however, are significant common factors influencing the efficacy of psychotherapy, independent of the therapy modality. Considerable variation exists in results concerning the effectiveness of psychotherapy in depression. A recent meta-analysis reported a mean effect size of 0.22 in high quality studies (Cuijpers et al., 2009; Cuijpers et al., 2010).

2.5.4 Combination of therapeutic modalities and duration of treatment

In most cases of depression, a combination of psychotherapy and pharmacotherapy is recommended. In a single episode of depression, pharmacotherapy is typically continued for six months after remission. In psychotherapy, the length of treatment ranges from a few months to several years. In recurrent depression, even lifelong pharmacotherapy, psychotherapy, or both, may be necessary. The effect size of combined therapies compared to pharmacotherapy alone is 0.43 (Cuijpers et al., 2014).

2.6 NEUROIMAGING AND PSYCHOTHERAPY IN DEPRESSION

At the beginning of the current study, only a handful of neuroimaging studies of psychotherapy existed. A more recent meta-analysis, however, found 90 studies which used different neuroimaging modalities (Weingarten and Strauman, 2014). Of these studies, 23 focused on the treatment of depression with different neuroimaging modalities. Functional magnetic resonance imaging (fMRI) was most widely used; SPECT and PET studies, mostly imaging blood flow, came next. Only two of the studies listed used ligands which bind with molecular targets, such as receptors or transporters. In a study by Karlsson et al. 2010, postsynaptic serotonin receptor 5HT1A binding increased after 16 weeks of short-term psychodynamic psychotherapy. A SPECT study with a slightly different ligand than ours, [123I] ADAM, found a bilateral increase of SERT availability in the medial temporal lobes after 12 weeks of cognitive behavioural therapy (Amsterdam et al., 2013).

Case studies (Viinamäki et al., 1998; Tolmunen et al., 2004; Saarinen et al., 2005), and a naturalistic six-month follow-up study (Laasonen-Balk et al., 2004), have suggested alterations in SERT availability related to clinical changes. Furthermore, atypical symptoms of depression were associated with change in SERT availability during psychodynamic psychotherapy (Lehto et al., 2008).

2.7 SUMMARY BASED ON THE LITERATURE

Multiple lines of evidence convergently point towards the importance of SERT in depression (Figure 6). Early simplistic models are replaced by novel views in which the 5-HT system, with the SERT as one of its modulators, is functionally connected with multiple factors associated with depression. This evidence includes findings assiociated with genetics, early nurture, neuroticism, environmental stress, cognition, emotional information processing, inflammation, and aging. The multitude of fragmental information seems logical, considering the widespread sertonergic network of the human brain. It is plausible that SERT relates to depression through mechanisms such as negative cognitive bias, thereby modulating vulnerability and resilience in the face of stressors, both psychological and physical. Although decreased SERT availability is associated with depression in cross-sectional neuroimaging studies, SERT availability does not seem to correlate with the severity of symptoms in mood disorders. Further evidence regarding the role of the SERT in depression comes from pharmacology. We know that agents blocking the SERT act as antidepressants. Despite a few preliminary studies, we still lack knowledge of how SERT availability changes in the absence of pharmacotherapy in either spontaneous recovery or psychotherapeutic treatment.

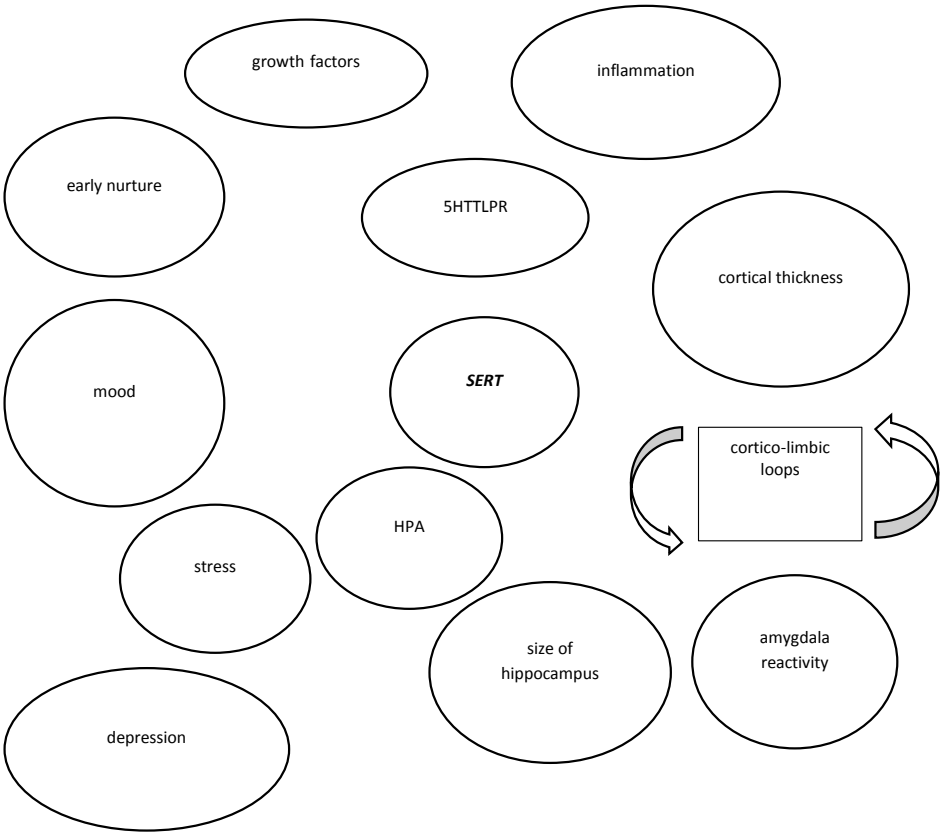

Figure 6. Significant factors associated with the function of SERT.

3 AIMS OF THE STUDY

The first two aims of the study concentrated on basic biological questions associated with the role of the SERT in depression while the third and main interest concerned neuroimaging of the effects of psychodynamic psychotherapy.

I

We first aimed to repeat earlier findings of SERT availability in depression on a sample larger than previous ones of drug-naïve subjects with a relatively specific SERT ligand.

II

Secondly, we explored the association of the 5HTTLPR genotype and the SERT phenotype in patients with MDD.

III

The third study question addressed the effects of psychodynamic psychotherapy on the SERT availability of unmedicated subjects. We repeatedly imaged SERT availability before and after both psychotherapy and waiting for psychotherapy. We also explored possible associations of clinical parameters of depression and SERT availability.

4 SUBJECTS AND METHODS

4.1 SUBJECTS AND STUDY PROTOCOL

Study subjects were referred to the outpatient clinic of Kuopio University Hospital from local health care centers and the student health care organization (Figure 7). We included drug-naïve, right-handed subjects with major depression. Exclusion criteria were psychosis, bipolar disorder, neurological disease, major somatic illness, substance abuse, and severe personality disorder. Potential study subjects were identified from the referrals and interviewed by psychiatrists of the research team by using the Structured Clinical Interview for DSM IV diagnosis (SCID) (Spitzer et al., 1992). The diagnosis was established at referral using SCID I, and the personality assessment was performed with SCID II after 12 months of psychotherapy treatment. The symptom severity of each participant was assessed at recruitment and after 12 months of treatment. The handedness of the study subjects was determined based on a questionnaire (Annett, 1967). The baseline patient group consisted of 24 women and five men with mean age (±S.D.) 28.8± 8.6.

The control group of the baseline study included comprised 16 women and three men. The group consisted of employees of Kuopio University Hospital and medical students. The control subjects were drug-free, right-handed, and subjectively healthy. The mean age (±S.D.) of the control group was 30.6±8.9.

The genetic study had 17 women and six men. The group was divided into SS-homozygotes (SS) and a group with at least one L allele (Lx). The mean age of the SS group was 28.0 and that of the Lx group 19.7. The female-to-male ratio was 6/1 in SS and 11/5 in Lx. The baseline symptoms with HAM 17 were 18.0 in SS and 18.8 in Lx.

Of the 60 referred patients, 54 were clinically assessed, of which 40 satisfied the criteria. During the waiting time, seven patients decided not to participate. Altogether, 33 patients (25 female, eight male) were included in the intention-to-treat analysis (Table 1). In order to assess the efficacy of psychotherapy vs. spontaneous recovery, every second referred patient was allocated to the direct therapy group (DG, n =17), starting psychotherapy directly after the assessment; the rest comprised the waiting group (WG, n =16), starting psychotherapy after an average of six months' waiting time (Figure 8). Five patients did not receive the allocated intervention. A total of 14 DG patients and 10 WG patients completed the study. Due to lack of clinical data, the number of patients in the final follow-up analyses was limited to 18.

4.2 MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) performed at the Kuopio University Hospital department of radiology was used to exclude structural brain abnormalities. We, furthermore, used MRI data as a structural map to identify regions of interest in the SPECT analysis.

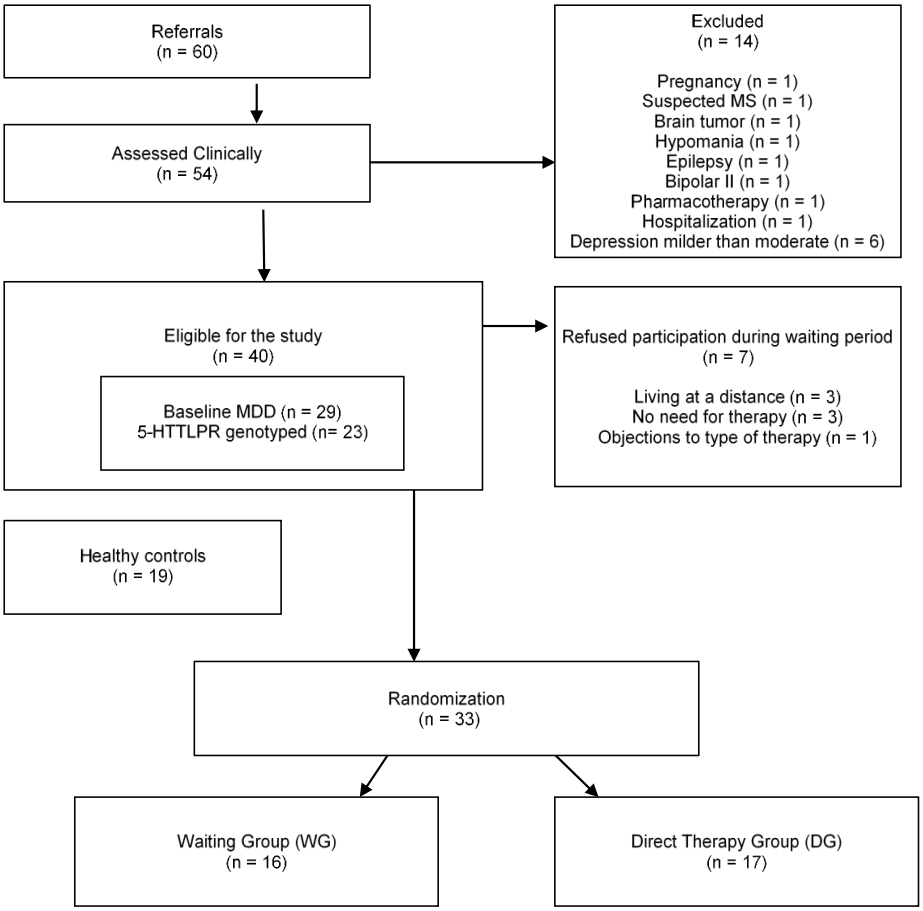

Figure 7. Flow chart of the material of all three studies.

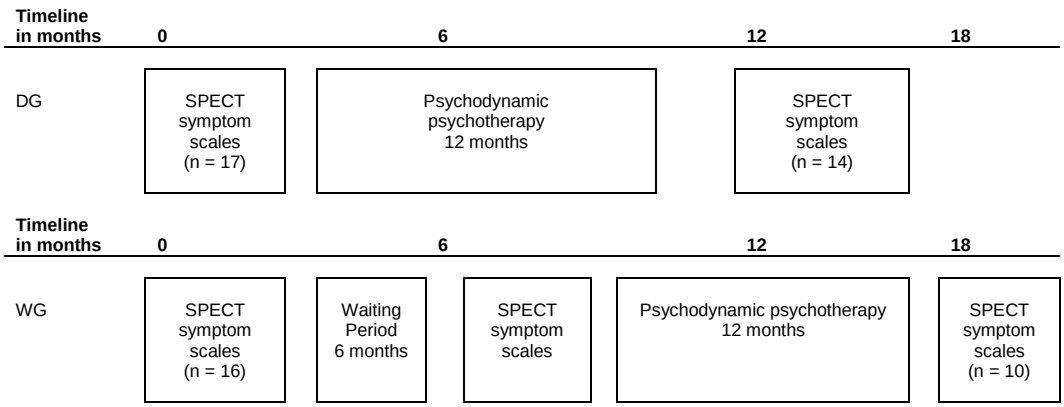

Figure 8. Protocol of the follow-up study.

4.3 CLINICAL SCALES

Depression symptom severity was measured by using the 17-item Hamilton Rating Scale for Depression (HDRS-17) (Hamilton 1960), the Beck Depression Inventory (BDI) (Beck and Steer 2000), and the Depression scale of the Symptom Checklist (SCL-90-DEP). Overall psychiatric symptoms were measured by using the Global Severity Index of Symptom Checklist (SCL-90-GSI). Anxiety symptoms were measured by using the Anxiety scale of the Symptom Checklist (SCL-90ANX) (Derogatis et al. 1973). Alexithymia measurements employed the Toronto Alexithymia Scale (TAS-20) (Bagby et al. 1994). Clinical evaluations were performed by experienced psychiatrists.

4.4 GENETIC ANALYSIS

The SLC6A4 genotypes were determined by polymerase chain reaction (PCR)-based sequencing. Genomic DNA was extracted from venous blood samples and amplified in 10μL PCR reactions containing 100ng genomic DNA, 5 pmol of a forward primer (5HTTforward: 5′-CGCTCCTGCA TCCCCCATTA-3′) and a reverse primer (5HTTreverse: 5′-GGGCTGCGGGGGAA TACTGGT-3′), 0.2 U of DyNAzyme II DNA Polymerase (New England Biolabs GmbH, Frankfurt am Main, Germany), and 0.2 nmol of each dNTP in buffer containing 60 mM Tris–HCl, 15 mM ammonium sulphate, and 2.0 mM MgCl2 (pH 9.0). Reaction conditions were 96°C for 2 min followed by 35 cycles of 96°C for 30 s, 63°C for 30 s, 72°C for 30 s, and a final extension step at 72°C for 5 min.

This resulted in the amplification of 296 base-pair (bp) fragments in the presence of 5-HTTLPR long form, and of 253 bp fragments in the presence of the short form. PCR fragments were purified for direct sequencing according to the instructions of the NucleoSpin Extract II (Macherey-Nagel, Düren, Germany). Sequencing was conducted with the ABI PRISM 3130xl Genetic Analyzer, using the 5HTT-reverse as the primer. 5-HTTLPR and the rs25531 single-nucleotide polymorphism (SNP) genotypes were determined from the chromatograms.

4.5 SPECT IMAGING AND DATA ANALYSIS

The ligand [123I] nor-β-CIT was provided by MAP Medical Technologies OY, Tikkakoski, Finland. A dose of 185 MBq with specific activity higher than 1.8×1011 Bq/μmol (Hiltunen et al., 1998), was diluted in 10ml of physiological saline and slowly injected into the antecubital vein in a dimly lit and quiet room. SPECT imaging was performed at 5 min, 6 h, and 24 h, after the injection, using a Siemens MultiSPECT 3 gamma camera with fan-beam collimators (Siemens Medical Systems; Hoffman Estates, IL, USA) (Kuikka et al., 1993). Two position lasers were used to control head positioning (Figure 9).

To control the possible effects of hormonal status, SPECT imaging for the women was performed on the first Wednesday after the end of menstruation, except for one patient who noticed that she was pregnant after SPECT imaging and three controls whose menstrual status was not controlled for technical reasons.

Decay correction reconstruction was performed with Butterworth-filtered back-projection in a 128×128 matrix with a pixel size of 3×3 mm2, and attenuation correction with Chang's algorithm (Hiltunen et al., 1998; Kuikka et al., 1993). The resolution of the imaging was 8–9mm. Summarized slice thickness was 6mm. The Siemens semi-automatic brain quantification program and Talairach coordinates (Talaraich and Tournoux, 1993) were used in re-aligning the slices and the placement of regions of interest (ROIs). To reduce volume averaging and partial volume errors, we used the lower threshold of 60% of the maximum count.

Our ROIs were the midbrain, medial prefrontal cortex, and cerebellum. The cerebellum as the reference region was assumed to correspond to a two-compartment model which has an unbound tracer in arterial blood and a free plus non-specifically bound tracer in the tissue. A graphical plot [(study ROI-Cerebellum)/Cerebellum= VD−1] was used to calculate specific binding in ml/ml for the SERT (Acton et al., 1999). The reproducibility of the imaging method was previously studied with 11 healthy subjects (five males and six females; age range 20–39), with SPECT imaging performed twice, with a 12-month interval. The correspondence between these two studies was good, with the mean difference (±S.D.) 0.00±0.08 for the SERT. One study had mean±S.D.: 1.27± 0.11 while the other had 1.27±0.14. The intraclass correlation coefficient was 0.82 (Pb 0.01).

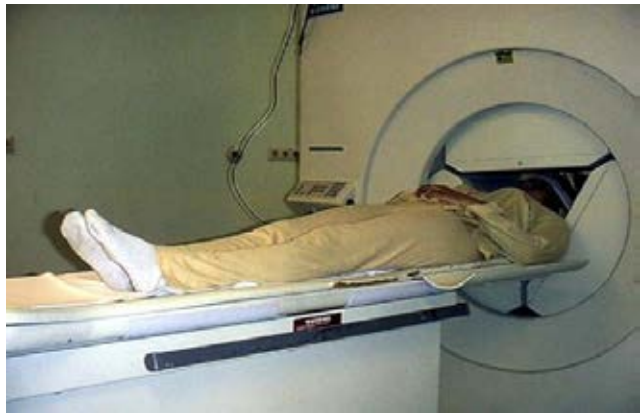

Figure 9. Siemens SPECT imaging at the Department of Clinical Physiology and Nuclear Medicine in Kuopio University Hospital (Photo courtesy of Jyrki Kuikka).

5 RESULTS

5.1 DECREASED SERT AVAILABILITY IN DEPRESSION IN MIDBRAIN (I)

We observed significantly lower SERT availability in the midbrain of depressed patients (1.15 ± 0.12 ml/ml, n=29), compared with control subjects (1.28 ± 0.11 ml/ml, n=19); independent samples t-test t=4.0, df=46, p=0.0002 (Figure 10). The medial prefrontal cortex (MPC), including the gyrus cingulum) exhibited no significant difference between patients with MDD and healthy controls. No correlation of SERT availability and symptom severity in any symptom scale emerged. Despite the significant statistical difference in the average SERT availability between healthy controls and MDD patients, numerous patients had higher SERT availability than the mean of that of healthy controls, indicating the heterogeneity of the MDD patients in this aspect.

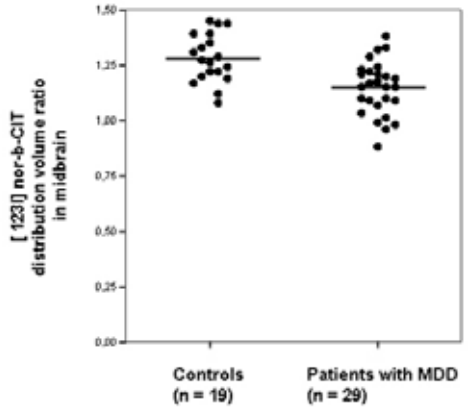

Figure 10. Distribution and ratio values of depressive patient and controls.

5.2 5HTTLPR GENETIC POLYMORPHISM AND SERT AVAILABILITY IN DEPRESSION (II)

There were no significant differences in age, gender or tha severity of symptoms between the different allelic groups. Subjects homozygous for the S-allele of 5-HTTLPR had lower SERT availability (0.20 ± 0.07 ml/ml), compared with other allelic variations (SL, Sla, LL, LaL, LaLa) (0.27± 0.05 ml/ml in the medial MPC. In the midbrain, the allelic groups had no significant difference (Two-way ANOVA type III, sum of squares: 0.022, d.f. = 1, P = 0.022) (Figure 11).

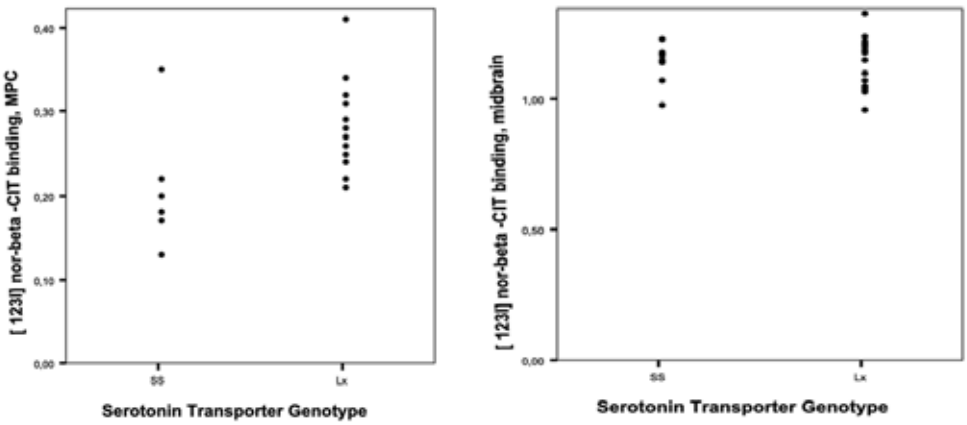

Figure 11. Distribution of volume ratio values in the midbrain and medial prefrontal cortex of depressed patients according to serotonin-transporter linked promoter region: SS homozygotes (SS) versus long allele (Lx) carriers.

5.3 BASELINE SERT AVAILABILITY AND SERT CHANGE DURING PSYCHOTHERAPY (III)

The change during the follow-up in midbrain SERT was predicted by the severity of baseline clinical symptoms measured with SCL-90 GSI (R = 0.58, P = 0.02, n = 18) and that of depressive symptoms measured with DEP (R = 0.60, P = 0.02, n = 18) (Figure 12). The patients with milder symptoms had decreased SERT whereas patients with severe global symptoms and depression had increased SERT availability during the follow-up, including waiting and psychodynamic psychotherapy.

Changes in symptoms and SERT availabilities during psychotherapy (Figure 13) had no correlation.

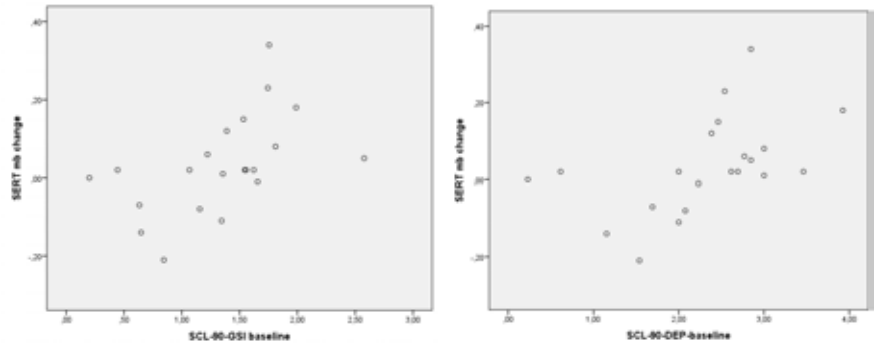

Figure 12. Change in midbrain serotonin transporter (SERT) availability and the Global Severity Index of Symptom Checklist (SCL-90-GSI) and Depression scale of Symptom Checklist (SCL-90-DEP) at baseline.

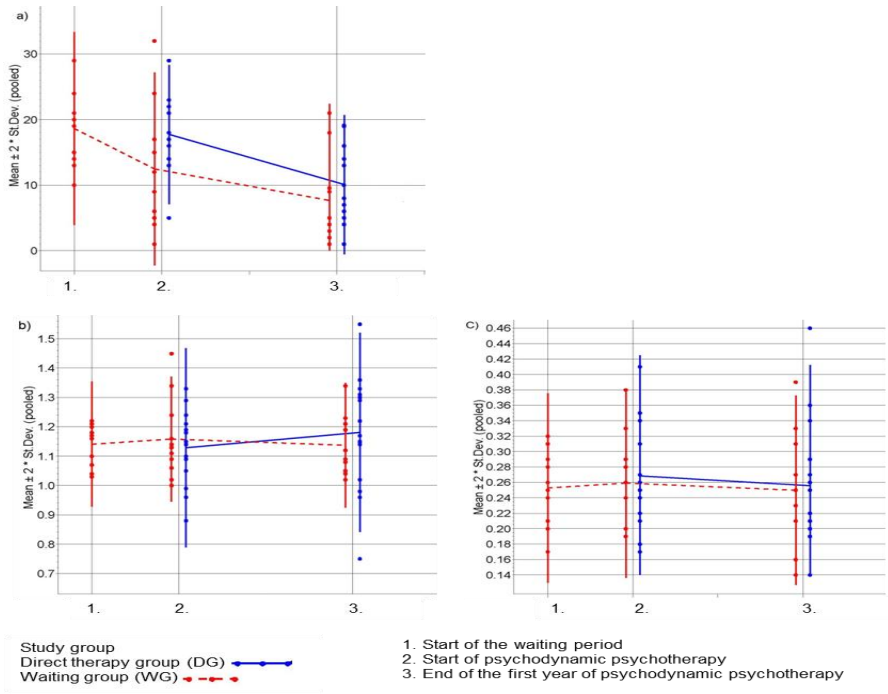

Figure 13. Change of a) symptoms of depression (HAM 17), b) SERT MB, and c) SERT MPC during the waiting period and the first year of psychodynamic psychotherapy. DG and WG groups are combined.

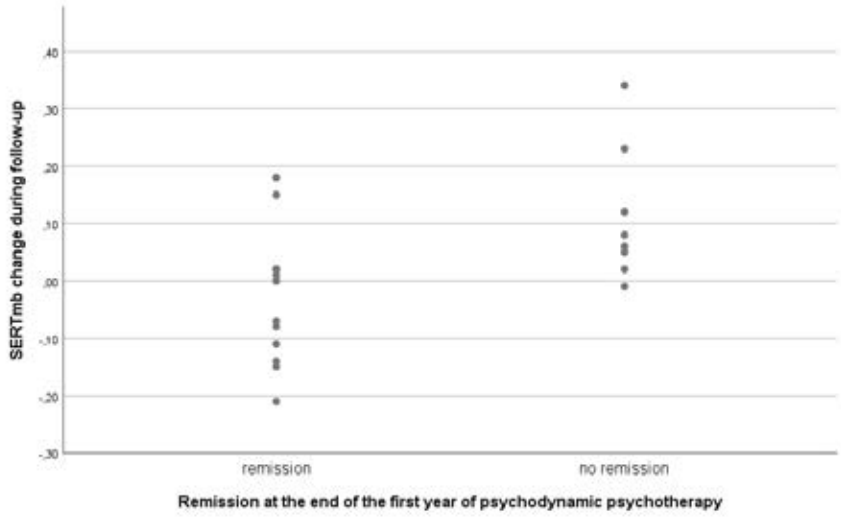

Figure 14. SERTmb change in patients dichotomized by remission criteria HAM17<12. (non-published data).

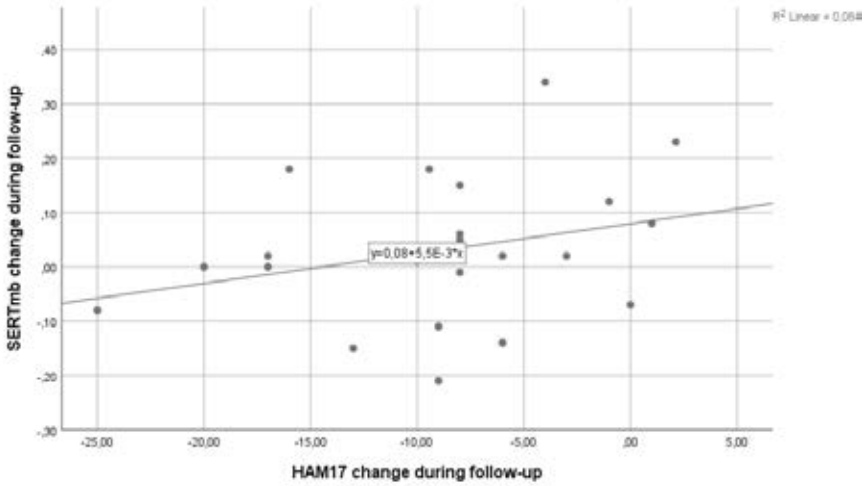

Figure 15. Change of HAM17 and SERTmb from baseline to the end of first year of psychotherapy. DG and WG groups are combined. (non-published data).

6 DISCUSSION

6.1 DECREASED SERT IN MDD

Our study provides significant evidence of the decrease of the SERT in the midbrain in major depression. This reduction is confirmed by a recent meta-analysis (Gryglewski et al, 2014). It is a seeming paradox that depressed patients, on average, have a deviance of the endogenous mechanism acting in the same direction as the functional effect of SSRI drugs. Possible explanations for the finding are several. The serotonin reuptake mechanism of depressed patients might be adapted to the level of synaptic 5HT or the other way around. A mathematical model suggests that, in connection with low SERT density, bursts of 5-HT neurons cause accumulation of 5-HT in the synaptic cleft (Best et al., 2010). In the 5-HT system, this might possibly be analogous with lower basal tone (tonic firing) of the circuitry. With the plasticity of the CNS, following the rule of "use it or lose it", lower firing of 5-HT neurons may reduce SERT availability. It is noteworthy that we do not even know whether 5-HT levels in depression are decreased or increased (Andrews et al., 2015).

It is also possible that decreased SERT availability reflects a homeostatic mechanism connected with stress coping (Houwing et al, 2017). In the future, multimodal imaging techniques will possibly answer some key questions, especially ones concerning causal relationships. Simultaneous measurement of synaptic serotonin levels, number and density of synapses, and reuptake, could answer some of the fundamental questions raised by the findings so far.

From the perpective of neuroimaging, the heterogenous diagnosis of depression may not be optimal. As the diagnostic criteria of depression may be fulfilled with multiple combinations of symptoms, the validity of the diagnosis has been subject to critique (Fried, 2017).

Although reduced midbrain SERT levels in depression have been confirmed in meta-analyses, it is noteworthy that this reduction is only evident when comparing large enough groups of patients with healthy subjects. The overlap in SERT availabilities of depressed patients and healthy subjects is considerable. This clearly implies that SERT imaging, at least currently, is not useful as a diagnostic tool of depression.

Our ROI in the midbrain is a phylogenetically well-preserved key structure with abundant connections in multiple brain areas needed in the experience of self. Alterations in the activity of these brain structures influence a wide variety of emotional and cognitive functions, some of which are associated with the syndrome of depression (Damasio, 1999).

6.2 DECREASED SERT LEVELS ASSOCIATED WITH SS-HOMOZYGOSITY

Genetic studies have pointed towards an association of the SERT promoter genotype and vulnerability to depression. Studies on twins of depressed patients and subjects with a family history of depression have found decreased SERT binding. Studies combining genotyping and molecular imaging, however, have found no correlations. Our sample was drug-naïve and ethnically homogeneous and included by chance many individuals with the 5HTTLPR genotype, SS. This group differed from the rest of the genotypes with decreased SERT binding in the prefrontal cortex. Studies with different modalities point toward the modulatory role of 5HTTLPR in cortical structure and function. Subjects homozygous for the S-allele have weaker connectivity in the corticolimbic loops (Pezawas et al., 2005). The S-allelle is also associated with reduction in short intracortical inhibition in magnetic stimulation associated with excitability of the cortex (Langguth et al., 2009). A modulatory role of 5HTTLPR exists also for cortical thickness (Bansal et al., 2016) and cortical brain resting blood flow (Rao et al., 2007). A plausible explanation for our finding is that it reflects the effect of the SERT promoter genotype on a molecular level in the medial PFC, a brain area connected with circuits vital to emotional processing. Modest evidence to date suggests that the SERT is associated with genetic variation of vulnerability, which could be mediated through differences in corticolimbic loops and cortical control of emotional processing (Heinz et al., 2005; Johnstone et al., 2007; Volman et al., 2013; Erk et al., 2010).

If decreased SERT availability is a sign of adaptation, it is interesting and somewhat contradictory that the genotype considered most vulnerable has even lower cortical SERT availability. Different functioning of the SERT in various areas of the brain might explain this seeming discrepancy. It is of interest that we failed to see any effect of genotype on midbrain SERT - the variable separating the healthy and the depressed.

The scale of the adaptational apparatus might have a critical role. The fact, that an initially higher SERT-expressive genotype benefits more from SSRI blocking seems to suggest that more potential for change exists, more to be blocked or downregulated. As high SERT-expressive genotypes are more resilient against depression, it can be indirectly assumed that SERT is part of an endogeneous adaptative mechanism. It is also possible that genetic vulnerability to depression functions in different ways, as do pharmacological and non-pharmacological compensatory mechanisms alleviating depression.

With a small sample and a study design concentrating on the effects of psychotherapy, we were unable to assess the possible interactions of genetic and environmental factors. Lack of early nurture or stress either independently or in interaction with inherited genetic variance may cause decreased SERT expression. This, in turn, leads to neurotic behaviour and decreased adaptive capacity in the face of novel stressors such as losses of significant objects and behavioral shutdown presented as clinical depression.

Although this polymorphism seems to modulate vulnerability to depression and brain functions connected with stress, neuroimaging studies correlating genotype and phenotype have produced mixed results. As our sample was small, this finding of decreased SERT in the MPC in the SS genotype must be considered preliminary. Larger multicenter studies will probably address this question more accurately in the future. Ethnic genetic differences, however, may cause problems for multicenter studies; an interplay of genetic and cultural adaptation and depression vulnerability may exist. Different cultures associated with variation in interpersonal styles, as well as different inherited neuroadaptation, may affect individual risk of developing depression.

Cortical SERT is, however, not significantly decreased in depression, compared to that of healthy controls. This lack of significant difference may relate to technical difficulties

in cortical SERT imaging. Midbrain SERT lacks an association with genotype but is, on average, decreased in patients with depression. Some evidence suggests that the relative availability of the SERT in different brain areas is more important than local serotonin tranporter availability. In MDD, availability in the striatum and raphe nucleus lacks correlation (Hahn et al., 2014). This relative availability seems also to predict treatment response to antidepressants. Patients with higher SERT availability in the habenula and amygdala in relation to the dorsal raphe were more likely to benefit from SSRI treatment (Lanzenberger et al., 2012). Further evidence for a disproportional function of serotonergic circuits of the cortex and midbrain comes from a recent autoradiography study in suicide victims. That study found the lack of correlation of both cortical 5-HT1A and 5-HT2A with raphe SERT densities and reduced cortical SERT density (Underwood et al., 2018).

6.3 HIGHER INCREASE OF SERT LEVELS DURING FOLLOW-UP IN PATIENTS WITH INITIALLY SEVERE SYMPTOMS

In our longitudinal study involving drug-naïve and unmedicated depressed patients during waiting and psychodynamic psychotherapy, we observed individual changes in SERT availability. These changes, however, had no associations with simultaneous changes in symptoms. Although the severity of depression failed to correlate with SERT availability cross-sectionally at any time point of SPECT imaging, the change in SERT availability during follow-up correlated with the severity of the overall symptoms and the severity of depression at the beginning of the study. Patients with high scores of symptoms at baseline had the highest increase in SERT availability during psychotherapy and recovery. This could be interpreted as indirect evidence for the role SERT availability has in homeostatic regulation. The correlation reached clinical significance only after our combining the waiting group and the group with direct start of psychotherapy. Thus, we cannot claim that the correlation observed had a specific association with psychotherapy.

A mere shift toward normal fails to explain the correlation of severity and change in SERT availability. Genetic research underlines the trait connected with 5HTTLPR, and animal studies have shown interactions of genotype and early rearing (epigenetic factors) producing vulnerability trait phenotypes. Our finding indicates that the SERT also has a state component. This state may be associated with stress factors initiating depression or the state of depression itself. Alleviation of this stress, either through specific effects of psychotherapy or other intrinsic or environmental factors, may alter the state-dependent component of SERT homeostasis. Midbrain SERT availability is associated with subjectively perceived social support (Huang et al., 2013) and self transcendence (Kim et al., 2015). These findings suggest that, besides genetic and epigenetic factors, one's relation to others and the outside world may play a crucial role in the modulation of serotonin reuptake. Psychotherapy could be considered as a rationally planned, influential environmental factor, requiring the active engagement of the patient in the process. If the theory of serotonin resistance proves right, we may speculate what would happen in the endogenous mechanism if stress was decreased by means of the top-down method of psychotherapy. We must note, however, that the increase in SERT levels had no association with alleviation of the symptoms of depression. Patients with increase of SERT availability tended not to reach remission. (Figures 14 and 15, non-published data). We can speculate that this could be a sign of fatigue of the biological coping mechanism; due to the small sample size, however, this interpretation remains speculative.

If relative change in SERT availability in different brain regions is the key to successful recovery, it is unfortunate that, with the limitations of current pharmacological methods, drugs administered in the blood reach all parts of the brain. Advanced neuromodulation

and psychotherapy, however, can, in theory, stimulate or inhibit brain regions more selectively. It has been, probably in a simplified way, suggested that psychotherapy functions in a top-down fashion, compared with pharmacotherapy exerting its effects bottom-up. The intuitively rational theory of disturbed interregional balances of brain networks might guide both biological and psychological treatment strategies and choices between treatment options.

In an earlier study with a subsample of the current study, subjects' atypical symptoms correlated similarly to how global symptoms do, with the change in the SERT during follow-up (Lehto et al., 2008). The atypical score correlated in that sample positively with the overall symptoms and depression symptoms (non-published data). We can argue that atypia and overall depression are mutually confounding factors.

During the follow-up, most of our patients recovered, but the alleviation of depressive symptoms had no correlation with the change of SERT availability. One interesting finding is the heterogeneity in reaching recovery regarding changes in SERT availability.

We started the study project with the assumption that SERT availability is associated with severity of symptoms as a biomarker of depression. During the study, the concept changed towards the idea that 5-HT function, and SERT availability as one part of that, is associated with a defence or buffer mechanism trying to cope with the allosteric load of stress. We could even postulate a simplified formula: symptoms = stress – buffer (Figure 16). Depression would then be a failure of compensation. As stressors are not commensurate, we cannot expect SERT availability to correlate with symptoms. As the endogenous stress buffer mechanism and social support may balance each other, simply too many uncontrollable variables exist in the equation for a strong correlation. It is possible that sensitive, neurotic individuals need and seek more social support; on the other end of the spectrum, individuals with hyperactive biological defence mechanisms are "immune to stress" and some are even prone to antisocial strategies.

Recent theories with focus outside of the monoamine function, such as those describing inflammatory mechanisms or growth factors, have been prominent in the biological explanation of depression. Our studies focused on no such associations, but literature shows that inflammation is essentially connected with serotonin function and that the interactive modulation of inflammation and SERT is evident. This means that the monoamine theory is not contradictory to other important etiological factors and, in many aspects, the complementary factors have known interactions.

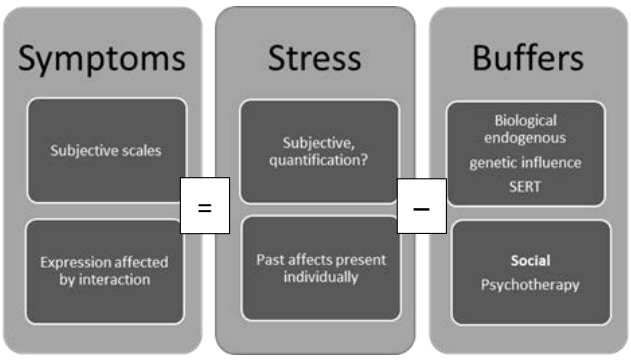

Figure 16. Simplified and theoretical model of a hypothetical role of the SERT in relation to stress, buffer mechanism, and symptoms.

6.4 LIMITATIONS AND STRENGTHS

The strengths and weaknesses of the three studies included in the thesis are discussed in the separate articles, but some of the most important points are underlined below.

6.4.1 Baseline (article I)

The age- and gender-matched group of healthy controls consisted of employees of the Kuopio University Hospital and students of the University of Eastern Finland. This restriction of the socioeconomic background of the control subjects may represent a source of bias.

6.4.2 Genetic study (article II)

In the genetic study, the small sample size was an obvious limitation. Due to statistical reasons, instead of comparing all the allelic variations, we had to limit the analysis to the SS group vs. others. Fortunately, compared to the general distribution of the alleles, we observed an overrepresented number of individuals with the SS genotype. This overrepresentation made it possible to unravel the difference in SERT availability. However, due to the small number of subjects studied, we have to consider the findings as preliminary. As the difference in SERT availability was found in the MPC, we have to bear in mind that SPECT imaging with our ligand in this region was connected with more methodological uncertainty than that of the midbrain. From the point of view of the genetic study, the homogeneity of the Finnish population is advantageous.

6.4.3 Follow-up (article III)

In the follow-up, we again had a limited sample size and the possible effects of selection bias. Further selection of patients suitable for non-pharmacological treatment may have occurred during the process, for example through drop-offs. The complex waiting-group protocol was necessary as we aimed to separate the effects of spontaneous changes and the effects of psychotherapy, in clinical and neuroimaging parameters. These subgroups had to be reunited for the analysis of total follow-up time, and this resulted in differences in the timing of the clinical examination and imaging (DG 12 months vs. WG 18 months). As this arrangement resulted in the imaging of the WG group in two seasonally opposing time-points, we cannot completely rule out the effect of seasonal variation. The relatively homogenous treatment model and training of the therapists must be considered a strength in the study setting.

6.4.4 General

The limited spatial resolution and tracer specificity of our SPECT imaging technique concerns all our three studies. The treatment naïveté of the study subjects could be seen both as a strength and as a limitation. When measuring SERT availability, the size of the serotonergic region was not controlled for. Volume decreases of some regions such as the hippocampus occur in depression. (Videbech & Ravnkilde, 2004) Another explanation for reduced binding of the ligand might be increased binding of endogenous serotonin. In some postmortem studies, serotonin washout, however, had no effect on decreased SERT binding. With treatment-naïve subjects, the biological mechanisms associated with the etiology and recovery of depression might be less confounded by earlier interactions. On the other hand, however, the individuals who choose drug-free treatment may not represent the average population of depressed subjects.

The combination of different viewpoints (genetics, psychotherapy) in this thesis may be seen both as incoherence or versatility.

7 SUMMARY AND CONCLUSIONS

7.1 MAIN FINDINGS

Although the role of serotonin in depression is complex and it seems to explain only a part of the disease, our baseline finding of decreased SERT levels in depression further underlines the modulatory role of the serotonin transporter in depression.

The preliminary finding of lower SERT availability in the MPC in patients homozygous for the S-allele of the 5HTTLPR may express one of the genetic mechanisms of vulnerability to depression.

In the follow-up study, we aimed to see the effects of psychotherapy on SERT availability. Following preliminary case studies and one naturalistic follow-up study, we assumed that reduced SERT availability is a biomarker of depression. We expected a normalization of this initial SERT reduction in connection with symptomatic recovery during psychodynamic psychotherapy.

It seems, however, that SERT availability fails to correlate with the severity of symptoms or change of symptoms. When measuring the effects of psychotherapy with neuroimaging, we need more thorough knowledge concerning the biological etiology of the clinical variables measured.

7.2 CLINICAL IMPLICATIONS

Our finding of overall reduction and -on the other hand, heterogeneity in SERT availability suggests that, from the serotonergic perspective, a need for individualized treatment exists. Subclassifications may be necessary for rational treatment planning. Neuroimaging is likely to become more available in the future, and we should try to base our treatment choices on facts. Depressed patients are rightfully frustrated when clinicians force them to participate in consecutive trials. Often, errors with different treatment modalities occur. Recent findings support attempts to make a rational choice between pharmacological treatment and psychotherapy, both choices based on biomarkers in depression (Chakrabarty et al., 2016; Dunlop et al., 2017).

The severity of MDD in our study was, in most cases, moderate. Although the use of pharmacotherapy has broadened from the most severe cases to milder symptomatology, the effectiveness of SSRI medication has been more modest in groups of patients with mild to moderate depression (Kirsch et al., 2008). This underlines the need for studies of also other treatment options.

Reduced cortical control of the amygdala affected by the 5-HTTLPR polymorphism can be volitionally compensated (Schardt et al., 2010). This finding and our follow-up data suggest that the mechanisms of depression connected with SERT function are sensitive to changes and can be modified also with non-pharmacological approaches. In old-fashioned computer analogy, this variation in the human hardware may be compensated through alterations in the software.

7.3 IMPLICATIONS FOR FUTURE STUDIES

In small steps, we have moved closer to an understanding of the role of the SERT in depression. Still, many unanswered questions exist, waiting for ever-evolving imaging methods. Topographical accuracy has been improving with ultra high-resolution PET (Cho et al., 2008). New diagnostic perspectives, endophenotype classifications, multicenter studies, long follow-ups, and even cohort studies combining different

neuroimaging modalities, are going to solve many puzzles. Recording perceived stress, and coping and defence mechanisms, may prove to be valuable in future neuroimaging studies of the serotonergic system. When attempting to view the biological changes associated with psychological change in psychotherapy, we must understand the mechanisms involved with the parameters measured. In many fields of science, "deus ex machina" has been recently invoked. In particular, image interpretation has benefited from artificial intelligence, including machine learning. It will certainly be useful in the recognition of complex patterns of neuroimaging, symptoms, endophenotypes, and treatment effects. Correlates of neuroimaging and long-time course of the disease and treatment choices will later help us in customizing treatment without speculating.

We must appreciate and honour the whole complexity of the functions of the mind in depression. Thus, futher studies of all pathophysiological factors, therapeutic modalities, and environmental factors, not only those that are easy to sell to customers, are obviously warranted.

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MIKKO JOENSUU

The serotonin system is relevant to depression, and modern antidepressants target the serotonin transporter (SERT). SERT availability in depressed patients was decreased when compared to healthy controls. This finding was affected by the genotype 5-HTTLPR. The change in SERT availability from the time of diagnosis to the end of psychodynamic psychotherapy was also correlated with the severity of baseline symptoms. Connections between SERT and depression have been made, and further research will deepen the understanding of this relationship.

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