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BRAIN IMAGING STUDIES IN SEVERE SOMATIZATION

by

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ABSTRACT

Mika Hakala

Somatization was described 4000 years ago but the pathophysiology of the phenomenon is unknown.

The aim of this investigation was to explore whether central nervous system (CNS) pathology is associated with severe somatization which was operationalized as somatization disorder (SD) and undifferentiated somatoform disorder.

The study sample consisted of severely somatizing people who were included into the study after a multi-phase screening procedure in order to exclude psychiatric comorbidities and physical illnesses. Diagnosis of somatization disorder or undifferentiated sofatoform disorder were set according to Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV).

The first study explored the regional cerebral metabolic rate of glucose (rCMRGlc) in severely somatizing females and found it to be reduced in several regions of the brain compared to healthy controls. The second study observed brain morphology with magnetic resonance imaging (MRI) based on the findings from the first study and showed enlarged caudate nuclei in somatizing women compared to healthy volunteers. The third study investigated temperament factors and brain metabolism, and their association with severe somatization. Low caudate and putamen metabolism, low novelty seeking as well as high harm avoidance were found to be associated with severe somatization in women, reduced caudate metabolism having the strongest association. The last study is a report of man with left-side gradient of multiple symptoms of unknown origin in the body. The examination revealed a hypermetabolic nucleus putamen on the contralateral side. All the main results reported in these four articles are original findings.

The results suggest that CNS pathology is involved in the pathophysiology of severe somatization.

Keywords: Metabolism, MRI, PET, Somatization, Temperament

Mika Hakala
AIVOJEN KUVANTAMINEN VAKAVASSA SOMATISAATIOSSA. Turun yliopisto, psykiatrian oppiaine. Annales Universitatis Turkuensis SARJA-SER. D – TOM

TIIVISTELMÄ

Mika Hakala

Somatisaatio kuvattiin jo 4000 vuotta sitten, mutta ilmiön patofysiologia on pitkälti tuntematon.
Tutkimuksen tavoitteena oli selvittää ja tutkia mahdollisen keskushemostopatologian yhteyttä somatisaatiohäiriöön ja erilaistumattomaan somatoformiseen häiriöön.

Tutkimusjoukko koostui vaikeasta somatisaatio-ongelmasta kärsivistä henkilöistä ja moniosainen haastattelu/selvitysprosessi oli edellytys tutkimukseen osallistumiseen psykiatristen ja fyysisten samanaikaisten sairauksien poissulkemiseksi. Somatisaatio-häiriön tai erilaistumattoman somatoformisen häiriön diagnoosi arvioitiin ja asetettiin Amerikan Psykiatriyhdistyksen DSM-IV diagnostisten kriteerien käsikirjan 4. version edellytysten mukaisesti.

Ensimmäisessä tutkimuksessa selvitettiin aivojen alueellista sokerimetaboliaa vaikeasti somatisoivilla naisilla ja sen todettiin olevan alentunut useilla aivojen alueilla terveisiin kontrollihenkilöihin vertailtaessa. Toinen tutkimus havainnoi aivojen morfologiaa magneettikuvauskameralla ensimmäisen tutkimuksen tulosten pohjalta ja havaintona todettiin suurentuneet caudatus-tumakkeet (caudatus l. häntätumake) somatisoivilla naisilla terveisiin vapaaehtoisiin verrattaessa. Kolmas tutkimus selvitti temperamenttitekijöiden ja aivojen sokeriaineenvaihdunnan yhteyttä vakavaan somatisaatioon. Alhainen tyvitumakkeiden (häntätumake ja putamen l. aivokuorukka) metabolia ja persoonallisuusdimensioista alhainen ärsykehakuisuus sekä korkea turvallisuushakuisuus olivat yhteydessä vakavaan somatisointiin. Alentuneen caudatus-aineenvaihdunnan yhteys oli selvin. Viimeinen tutkimus on tapausselostus monioireile-vasta miehestä, jolla oireilu painottui kehon vasemmalle puolelle. Tutkimus paljasti kontralateraalisen (oikean) puolen putamen-tumakkeen ylitoiminnan aivoissa. Tulokset ovat alkuperäishavaintoja.

Tulosten perusteella keskushermostopatologia on yhteydessä vakavan somatisaation patofysiologiaan ja oireiluun.

Avainsanat: Aineenvaihdunta, MRI, PET, Somatisaatio, Temperamentti

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ABBREVIATIONS

ARC	American College of Rheumatology
B.C.	Before Christ
CD	Conversion Disorder
CFS	Chronic Fatique Syndrome
CNS	Central Nervous System
DA	Dopamine
CO	Co-Operativeness
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECA	Epidemiologic Catchment Area Study
[18]FDG	[18F]-Fluorodeoxyglucose
FM	Fibromyalgia
FWHM	Full Width at Half Maximum
GM	Gray Matter
HA	Harm Avoidance
IC	Informed Consent
ICD	Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death
IEI	Idipathic Enviromental Intolerance
LC	Lumped Constant
MDD	Major Depressive Disorder
MPR	Magnetization Prepared Rapid Gradient Echo
MUS	Medically Unexplained Symptom
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
NS	Novelty Seeking
NFBC	Northern Finland Birth Cohort
P	P-value, Probability value
PD	Personality Disorder
PET	Positron Emission Tomography
PS	Persistence
PTSD	Post Traumatic Stress Disorder
PVE	Partial Volume Effect
rCBF	Regional Cerebral Blood Flow
rCMRGlc	Regional Cerebral Metabolic Rate of Glucose
RD	Reward Dependence
RF	Radio Frequency
ROI	Region of Interest
SAS	Statistical Analysis System
SCID	Structured Clinical Interview
SCL	Symptom Checklist
SD	Self-Directedness, Somatization Disorder
SPECT	Single Photon Emission Computed Tomography

SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
ST	Self-Trancendence
T	Tesla (1000 gauss)
TCI	Temperament and Character Inventory
TPQ	Tridimensional Personality Questioinnaire
1H	Hydrogen
2D	Two-dimensional
3D	Three-dimensional
13C	Carbon
23Na	Sodium
31P	Phosphorus
39K	Potassium

LIST OF ORIGINAL PUBLICATIONS

1. Hakala M, Karlsson H, Ruotsalainen U, Koponen S, Bergman J, Stenman H, Kelavuori J-P, Aalto S, Kurki T, Niemi P: Severe somatization in women is associated with altered brain glucose metabolism. *Psyhological Medicine 2002 Nov; 32(8): 1379-85.*

2. Hakala M, Karlsson H, Kurki T, Aalto S, Niemi P, Koponen S: Volumes of the caudate nuclei in women with somatizing disorder and healthy women. *Psychiatry Research; Neuroimaging 2004 May; 131: 71-78.*

3. Hakala M, Vahlberg T, Niemi PM, Karlsson H: Brain glucose metabolism and temperament in relation to severe somatisation. *Psychiatry and Clinical Neurosciences 2006 Dec; 60: 669-675.*

4. Hakala M, Hirvonen J, Karlsson H: Back to Briquet and Charcot. *CNS Spectrums 2008; 13(7): 550-551.*

1. INTRODUCTION

Somatization is a common problem seen especially by general practioners and many somatizing patients are frequent attenders in health care establishments (Escobar et al. 1987b, Karlsson et al. 1997). The condition is seen across different cultures and health-care systems and yields considerably high health-care costs (Kirmayer and Young 1998, Lipowski 1988, Quill 1985, Smith et al. 1986). The term "somatization" stems from word *soma* referring to the body. Additionally, terms somatic, somatoform and psychosomatic refer to: of the body, bodylike and union of the mind and the body, correspondingly (Chaturvendi and Desai 2006). Subjects suffering from severe somatization perceive themselves ill, and The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) suggests that somatoform disorders are defined by the presence of physical symptoms that suggest a general medical condition but that are not fully explained by a general medical condition, by the direct effects of substance, or by another mental disorder. The symptoms must cause clinically significant distress or impairment in social, occupational or other areas of functioning. In contrast to factitious disorder or malingering, the symptoms are not under voluntary control (APA 1994). Somatizing patients may be considered difficult or frustrating to physicians and this may lead to problems in patient-physician relationship (Hahn et al. 1996, Hartz et al. 2000, Jackson and Kroenke 1999, Kroenke 2000, Lin et al. 1991, Lynch et al. 2007).

Severe somatization in this study is operationalized as somatization disorder (SD) and undifferentiated somatoform disorder according to DSM-IV criteria. Despite the problems mentioned above, the etiology and pathophysiology of severe somatization has remained an area where different theories have been postulated but no definitive answers have been established. Research has focused on areas other than biological factors. Brain imaging techniques, in addition to other means of investigation may generate additional information of the biomarkers and the nature of the disorder(s). To facilitate the detection of possible underlying mechanisms of these disabling conditions, more data is needed to address the factors influencing them, and further, enable the development of meaningful and targeted treatment options. In the present study the possible underlying pathology of severe somatization was explored in a patient sample using imaging techniques in addition to clinical and neuropsychological assessments. Other medically unexplained symptoms (MUS) such as chronic fatigue syndrome (CFS), fibromyalgia (FM), among others, also require clarification in relation to somatoform disorders.

2. REVIEW OF THE LITERATURE

2.1 HISTORY AND DIAGNOSIS OF SOMATIZATION

Hysteria was first documented 4000 years ago by the Egyptians, who believed the symptoms originated from the uterus, hence the name (hysterus) (Ford and Folks 1985). Their idea was that a displacement of uterus caused the symptoms (Millon 2004). "Hysterical" conditions included combinations of seizures, paralysis, and anesthesia. According to Hippocrates (460-370 B.C.), the concept of hysteria was much the same as that described by the Egyptians (Howells 1975). Galen (129-199) also believed the hysteria was related to the uterus, but the retention of secretion analogous to male sperm was the reason for hysteria. Consequently, males were also prone to hysteria due to fact that their sperm retention was possible as well. The retention could result in poisoning of the blood or body cooling, and further, to hysterical attacks (Fink 1996). St Augustine (354-430) considered a hysteric person to be a human possessed by, or in league with the devil (Fink 1996). During the 17th and 18th centuries a variety of disorders, such as: hysteria, hypochondriasis, dyspepsia, "gas and spleen disease" (Vapours) were included in the general term – "Nervous Disorder", a term created by Briefe in 1603, that was subsequently replaced with the vague term "Nervous Temperament" (Hare 1991). Jordan (1603) described the brain to be the seat of hysteria (Fink 1996). Also Willis (1621-1675) regarded hysteria as a nervous disorder, and Sydenhamn (1624-1689) thought it to be a psychological disease of the mind, not of the body (Howells 1975). It is generally regarded that William Cullen (1717-1790) coined the term neurosis and sharpened the idea of nervous force to energy as applied to disease. The concept of neurosis was used to explain special forms of illness that concerned physicians as far back as Sydenham (Boss 1976, Bowman 1975, Lopez-Pinero 1983).

The modern age of nerve pathologies commenced in 1843, the year Emil du Bois Reymond (1818-1896) demonstrated electrical conduction in nerves. No electrical disturbances were found in the "Nervous Temperament", leading to the hypothesis of psychogenic origin (Mace 1992). The term "Hysterical Conversion" was created about 100 years prior to Freud's birth, in an attempt to justify the existence of hysteria as a diagnosis. The French neurologists, Babinski (1857-1932) and Charcot (1825-1893) were among the first to publish articles concerning hysteria in the modern literature. Lhermitte (1877-1959) wrote "hysteria is the mother of deceit and trickery". Babinski removed from hysteria some components, such as; secondary physical findings, malingering, self-injuries and pathological lies. He defined hysteria as a disease with a psychological etiology, and no clear physiological or morphologic evidence, and characterized the hysterics as hyper-suggestible and easy to hypnotize (Hare 1991, Mace 1992). Paul Briquet (1796-1881) was the first to make an association between conversion disorder (CD) and central nervous system disorders during the 19th century. He claimed CD was due to stress and environmental situations, affecting "affective" areas in the brain of a person with pre-morbid hypersensitivity (Mai and Mersky 1981).

His follower, Charcot, hypothesized that these patients were suffering from a global disorder of the brain, exposing them to the development of CD. He developed the primary description of hysteria and contributed to the understanding, diagnosis and management of this disorder. Lately, his work has regained recognition, when the component of his theory concerning the pathophysiology of trauma was introduced into the modern theories regarding post-traumatic stress disorder (PTSD) and Somatoform Disorder (White 1997).

Freud (1856-1939), a student of Charcot, defined "La Grande Hysterie", that overlapped the definition of motor paralysis. Freud's concept of conversion originated from an integration of medical thoughts and knowledge in this area during the 19th century, which led him to create the term "Conversion Neurosis". According to his traumatic model of hysteria, published in 1899, hysterical symptoms stem from sexual trauma, that activates an old traumatic event (Nachtriglichkeit). Freud argued that through analysis, the childhood trauma is restored and the neurotic symptoms released via a transfer mechanism (Makari 1997). History itself has provided evidence of women with extra-ordinary achievements, all of them with hysteria, such as Theresa of Avila and Florence Nightingale (Mace 1992). There are reports of mass hysteria, mostly during wars or crisis (Small et al. 1991). Also Adolf Hitler is worth mentioning, as suffering from hysterical blindness (Retief and Wessels 2005).

The second edition of the DSM (DSM-II) classified unexplained medical symptoms into neuroses, ten types of psychophysiologic symptoms, and special symptoms. Briquet's syndrome was also included in the DSM-II, and by definition, assumed the onset age being under 30 years associated with psychological distress and without any demonstrable physical etiology. Characteristic symptoms were frequent bodily pains, pseudoneurological conversion symptoms, gastrointestinal symptoms, sexual and menstrual problems, anxiety and depressive symptoms, and patients belief of being sick for most of their lives. Altogether 59 different potential medically unexplained symptoms were described in 10 categories and at least 20 symptoms of them in nine categories were required for diagnosis of Briquet's syndrome (APA 1968, Guze 1967, Perley and Guze 1962).

The third edition of DSM (DSM-III) transformed mental illnesses from broad, etiologically defined entities that were continuous with normality, to symptom-based, categorical diseases. Mental disorders with physical symptoms were separated from dissociative disorders, a new category. The mental disorders with physical symptoms class included somatoform disorders, containing conversion disorder, somatization, psychogenic pain, and hypochondriasis. Briquet's syndrome were renamed to Somatization Disorder. The diagnostic criteria included 12 symptoms for men or 14 symptoms for women out of 37 somatic symptoms. The former psychiatric symptoms were eliminated from the symptom list. (APA 1980, Hollifield et al. 2004).

The revised version of DSM-III (DSM-IIIR) classified somatization to somatization disorder, undifferentiated somatoform disorder, adjustment disorder with physical complaints, and somatoform disorder unspecified. SD was a chronic, undulating and

relapsing disorder with a presentation of multiple physical complaints in different organ systems without detectable organic pathology (APA 1987, Hollifield et al. 2004).

The current version of DSM-IV requires eight symptoms from four defined organ symptom groups to fulfill the diagnostic criteria of SD. A total list of 33 somatic symptoms is suggested to be typical for SD. Onset age under 30 years is also required, and at least two years duration of the symptoms (APA 1994).

The Eighth Revision International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-8) by World Health Organization (WHO) defined psychosomatic diseases as physical disorders of presumably psychogenic origin. These were divided according to organ systems (WHO 1968).

The ICD-9 was published in 1977. The neurosis section included conversion syndrome, hypochondrial syndrome and SD, among others. Psychogenic vomiting and chronic pain syndrome were put into the section: " not in another sections defined syndromes" (WHO 1977).

The current version, ICD-10, requires six medically unexplained symptoms in two separate symptom groups for diagnosis of SD, causing distress and consumption of medical services. Duration of the symptoms should be at least two years, but no definitive onset age has been determined. The emphasis is on persistent request for medical investigations in spite of negative earlier findings and reassurance by doctors of non-organic etiology of the symptoms, as well as exclusion of psychological causality (WHO 1992).

There are a variety of disorders defined as psychological, which may result in physical disability without any known medical basis. Confusion has arisen because of the number of terms and definitions, as well as overlap between historical and current terminology. While in the past the term hysteria was used in multiple contexts, the following terminology can be applied (Heruti et al. 2002):

1. Somatization Disorder – Classic historical hysteria (Briquet's syndrome)
2. Hysterical Neurosis – including: (a) Conversion Disorder (CD) and (b) Dissociative Disorder
3. Anxiety Hysteria – includes Freud's definition of phobia
4. Hysterical Personality – refers to a term that was later substituted by the term Histrionic Personality.

Most terms included in the above terminology are associated with the present term "Somatoform Disorder" (Heruti et al. 2002). The definitions used come from DSM-IV concerning a group of disorders, characterized by somatic symptoms not adequately explained by a disease, side effects of medication or due to any other psychological mechanism (ie. Panic Disorder) (APA 1994).

The Somatoform Disorders category has been a subject of controversy also after its introduction in the DSM-III and the debate continues as the next version of DSM

(DSM-V) is under development. The ability to cover the clinical phenomena has been questioned (Fava 1992, Kellner 1994, Mayou et al. 2005, Starcevic 2006). The ICD and DSM diagnostic criteria are also considered strict in clinical use for defining SD, but on the other hand somatoform disorder criteria are broad (Rief and Sharpe 2004). Criticism is pointed to the grouping which is considered to promote dualism, to assume psychogenesis, and that it contains heterogeneous disorders that lack validity. Diagnoses currently within somatoform disorders could be redistributed into other groupings, and the disorders currently defined solely by somatic symptoms could be placed on axis III as "functional somatic symptoms and syndromes". Greater use could be made of "psychological factors affecting medical condition" on axis I (Creed and Barsky 2004, Mayou et al. 2005). Fava and Wise have suggested a solution of "psychological factors affecting either identified or feared medical conditions" where the need of somatoform disorders section in DSM-V is eliminated (Fava and Wise 2007). On the other hand the classification of somatoform disorders as "mental disorders" could be justified if empirically founded psychological and behavioural characteristics are included into the classification process. Attention focusing, symptom catastrophizing, and symptom expectation are outlined as possible examples of involved psychological processes (Rief and Isaac 2007).

2.2 EPIDEMIOLOGY OF SOMATIZATION

2.2.1 Prevalence

The prevalence of SD based on several trials varies from 0.02% to 1.84% (Karvonen 2007).

Several diagnostic criterion were used; DSM-III, DSM-IIIR, DSM-IV, ICD-10, Briquet syndrome (Karvonen 2007). The largest single report was the epidemiologic catchment area (ECA), USA, where the prevalence was 0.13% by using a standardized and structured psychiatric interview technique, Diagnostic Interview Schedule (DIS) for DSM-III definition criteria assessment was used (Karvonen 2007). Karvonen et al. reported a prevalence of 1.1% for SD (Karvonen et al. 2004). Bass et al. suggested a "true" prevalence rate of 1% for SD (Bass et al. 2001).

The prevalence of somatoform disorders by using different alternative approaches has varied between 0.7% - 23.6% (Karvonen 2007).

2.2.2 Gender

It is generally accepted that women have more somatic complaints of unknown origin than men. This is supported by the observation that women have a higher somatization score and more somatic symptoms have been reported by some researchers (Escobar et al. 1987a, Garcia-Campayo et al. 1998, Hiller et al. 2006, Huurre et al. 2005, Swartz et al. 1989). However, the same number of symptoms in men and women were observed by Karvonen et al. (2007).

The female: male ratio has also been reported to be elevated in SD (Garcia-Campayo et al. 1998, Garyfallos et al. 1999, Robins et al. 1984, Swartz et al. 1986a, Swartz et al. 1986b, Swartz et al. 1989, Swartz et al. 1990). In the Northern Finland Birth Cohort (NFBC) studies Karvonen et al. reported 5:1 ratio in SD and 6:1 ratio in subject with somatizing symptoms (at least 4 symptoms) (Karvonen et al. 2004, Karvonen et al. 2007). The lowest gender (female: male) rate of lifetime prevalence of SD reported is 0.73:1 and the highest 29:1 in population based trials (Karvonen 2007).

2.2.3 Other sociodemographic variables

Higher prevalence of somatization symptoms has been reported to be associated with lower socioeconomic groups, rural residents, lower household income, lower education level, exposure to violation and unmarried persons (Creed and Barsky 2004, Eberhard-Gran et al. 2007, Escobar et al. 1987a, Garcia-Campayo et al. 1998, Hiller et al. 2006, Huurre et al. 2005, Karvonen et al. 2007, Robins et al. 1984, Swartz et al. 1986a, Swartz et al. 1986b, Swartz et al. 1989).

The number of somatic symptoms has been reported to increase as job strain index and job demand became higher (Nomura et al. 2007). Somatization might be a stress response with regard to increased distress severity and psychosocial stressors rather than a cultural response to express psychological problems in somatic terms (Mak and Zane 2004).

Patients with somatoform disorder had more primary care visits, more specialist visits, more emergency department visits, more hospital admissions, more ambulatory procedures, higher inpatient costs, and higher outpatient costs when compared with nonsomatizing patients (Barsky et al. 2005, Barsky et al. 2006). Somatization has also been found to be associated with benzodiazepine craving (Mol et al. 2005).

2.2.4 Co-morbidity with psychiatric illnesses

At least a third of patients with somatoform disorders have comorbid anxiety or depressive disorders. Depression and anxiety co-occur with one another up to 50% of the time (Fink et al. 2004, Henningsen et al. 2003, Kessler et al. 2003, Löwe et al. 2008, Toft et al. 2005).

Swartz et al. found that ECA respondents with a lifetime diagnosis of DSM-III somatization disorder, assessed with the Diagnostic Interview Schedule (DIS), had a much higher probability for having a lifetime history of DSM-III panic disorder (about 25 times higher), obsessive-compulsive disorder (about 12 times higher) and major depression (about 11 times higher) compared with those without this disorder (Swartz et al. 1990).

2.3 ETIOLOGY AND PATHOPHYSIOLOGY OF SOMATIZATION

2.3.1 Psychological theories

During the 19th century, hysteria and hypochondriasis, which had once been frequent diagnoses, all but disappeared as organic diseases were removed from the respective categories. For hysteria, these included tertiary syphilis and epilepsy, and, for hypochondriasis, they included gastrointestinal diseases. Toward the end of the century, hypochondriasis was subsumed under the broad category of neurasthenia, although it later reemerged as something distinct. At the same time, hysteria was popularized by Charcot, and it became a concern of psychoanalysis. According to Breuer and Freud, mental distress might be converted into physical dysfunction, symbolic of that distress. Consequently, such functional neurological disturbances became known as "conversion" symptoms (Beard 1880, Breuer 1956, Micale 1993).

In this theory it was suggested that a person does not react to the physical trauma during the actual situation, but represses it. Later on, the trauma will manifest itself in forms of physical symptoms – conversion. Essential was that abuse or sexual trauma was taking place in the phallic phase of child's psychosexual development. After a while the view was changed – reported traumas represented childhood fantasy (Freud 1981, Pribor et al. 1993). Kohut's basic hypothesis was that anxiety is caused by the threat of disintegration of the self. This model includes the idea that physical symptoms can be regarded as an unspecific reaction pattern without symbolic meaning (Kohut 1988).

Defense mechanisms of denial, displacement or rationalization allow turning away from unacceptable thoughts and situations towards a focus on physical problems. This might result in a person becoming preoccupied with his bodily problems instead of confronting personal intolerable conflict, but perhaps, avoiding depression or even more severe mental disorder (Bridges et al. 1991, Pilowsky 1978).

According to the interpersonal model of Stuart and Noyes, somatic symptoms represent care-seeking behavior on the part of individuals with insecure attachment (Noyes et al. 2002, Stuart and Noyes 1999). They, like Bass and Murphy, point to the importance of developmental factors both for shaping personality and for directing attention toward somatic symptoms (Bass and Murphy 1995). Experience with illness in oneself or one's family may be an important causal factor (Graig et al. 2004).

Stress-diathesis modeling provides yet another conceptualization for somatization and somatoform disorders. Some patients are vulnerable to somatic distress by virtue of their psychological make-up; they deviate from the norm on psychological dimensions (Dersh et al. 2002).

The model of emotional awareness includes the idea that somatization is a deficit in emotion processing, because experiencing feeling is a cognitive skill. Cognitive dysfunctioning has been reported in severe somatization (Lane and Schwartz 1987, Niemi et al. 2002)

Cognitive hierarchical models include the idea that functional complaints are, for example, ascribed to functional dissociations between the experience of volition and the control of thought and action. The symptoms arise when the chronic activation of symptom related "mental representations" stored in memory cause the lower-level attentional selection process of contention scheduling, to select inappropriate sensory information or motor programs, resulting in a misinterpretation of the sensory world or a lack of motor activation, respectively (Brown 2004, Oakley 1999).

Failure to filter input information is one theory in somatization. Patients have lower threshold for maladapted reactions to normal body sensations. These are misinterpreted to be a physical disease (Fink et al. 2005). Close to this idea is "somatosensory amplification" which is referring to cognitive experience of somatic sensations as pathological – intense, noxious and disturbing – in nature (Barsky 1992, Nakao and Barsky 2007).

The interpretation of physical sensations as a sign of illness leads to help seeking, which can in itself be a source of maintaining factors. Inadequate reassurance or negative doctor-patient interactions can increase the distress associated with symptoms. This multidimensional model integrates social responses, which include other health care providers, work conditions, insurance, and compensation systems. These social factors can reduce motivation to use self-help strategies and cope with symptoms (Kirmayer and Taillefer 1997).

Symptom attribution is a cognitive process giving meaning to sensed bodily symptoms. This symptom attribution can be normalizing, somatizing or psychological in nature depending on the meaning given to the sensation by the subject (Burton 2003).

Perception is essential to describe physical complaints. Two models focus on the perception process itself, namely Pennebaker's model of the psychology of physical symptoms, and the signal-filter model of Rief and Barsky (Figure 1) (Pennebaker 1982, Rief and Barsky 2005).

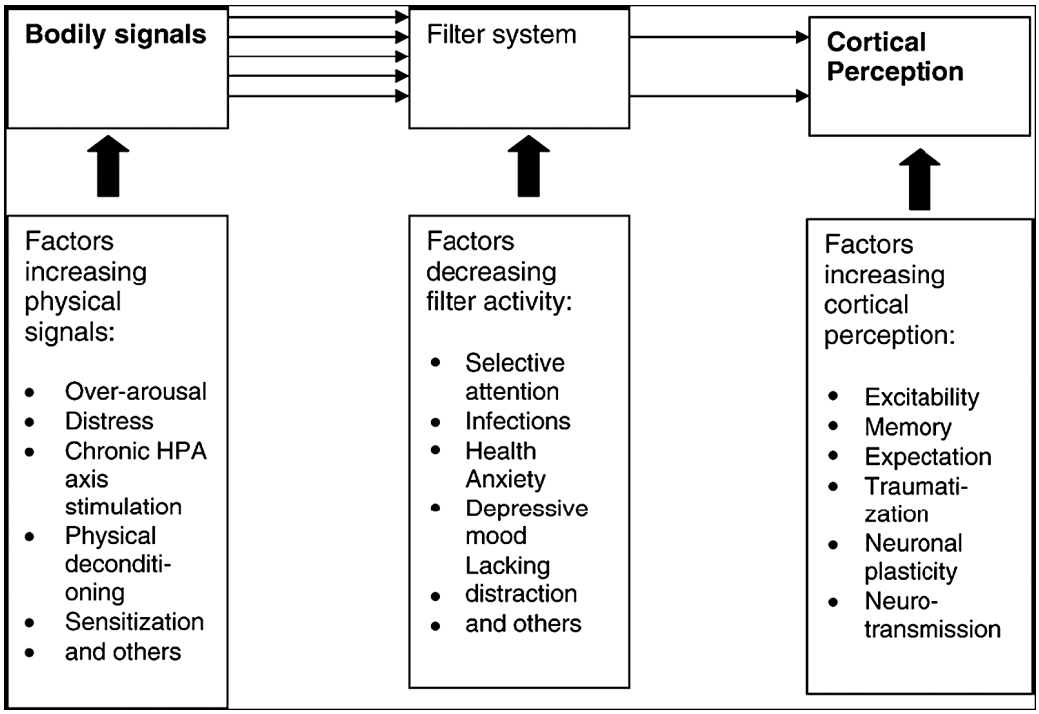

Figure 1. The perception-filter model of somatization (modified from Rief and Barsky 2005 in Rief and Broadbent 2007).

2.3.2 Illness behavior and severe somatization

Illness behavior has been a focus already by Mechanic (Mechanic 1962). Such behavior is appropriate for a person with physical disease occupying the "sick role" but, when such disease is lacking, it may be viewed as abnormal (Cooper 1999, Pilowsky 1969).

This kind of behavior may be a manifestation of disordered personality and high rates of personality disorders have been observed among somatoform patients (Bass and Murphy 1995, Stern et al. 1993). According to an interpersonal model for somatization somatic symptoms represent care-seeking behavior on the part of individuals with insecure attachment (Stuart and Noyes 1999).

Research has shown somatization to be associated with frequent use of health services (Ford 1992, Karlsson et al. 1997, Katon et al. 1991, Portegijs et al. 1996). Frequent medical attendance is associated with somatic symptoms, as well as with hypochondriasis and greater psychiatric comorbidity (Jyväsjarvi et al. 2001).

The attitudes of excessive health related worry, bodily preoccupation, a conviction of a more sinister disease related cause for symptoms and a fluctuating resistance to reassurance to the contrary may culminate in a process of frequent consultations for treatment and even requests for repeated investigations which, often do nothing to improve (and sometimes even perpetuate) the tendency to amplify and somatically

attribute otherwise innocuous symptoms. The result is a vicious cycle causing an extraordinarily high use of health care resources (Fink 1992a, Fink 1992b, Kolk et al. 2002, Rief et al. 2004b).

2.3.3 Temperament and somatization disorder

Several models have been proposed for classifying personality and temperament. These models like NEO 5-Factor Inventory, Temperament and Character Inventory (TCI), Eysenck Personality Questionnaire, Eysenck Impulsiveness-Venturesomeness-Empathy Scale and Sensation-Seeking Scale are used in clinical research and these personality traits build the basis of consistent patterns of experience and behavior (Muller et al. 2008). Cloninger's psychobiological model of personality – Temperament and Character Inventory - has been used in various clinical trials (Miettunen et al. 2008).

Cloninger's psychobiological model of personality consists of temperament and character factors and is a leading conceptualization of temperament. The four temperament dimensions; novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (PS), in particular, have attracted interest among researchers because they seem to be associated with clinical outcomes such as psychiatric disorders and precursors of somatic diseases (Cloninger 1987, Cloninger et al. 1993). High novelty seekers are characterized by impulsive decision-making and active avoidance of frustration. Harm avoidance is manifested as anticipatory worry, fear of uncertainty, shyness with strangers, and rapid fatigability. Individuals who are high in reward dependence tend to be sentimental, eager to help and please others, and warmly sympathetic. Persistence is measured in terms of perseverance despite frustration and fatigue (Cloninger et al. 1993).

Grabe et al. (2004) reported harm-avoidance to be associated with somatization when assessing alexithymia and personality in relation to dimensions of psychopathology. Russo's results revealed that the number of lifetime medically unexplained symptoms were significantly, independently, and positively related to increasing numbers of current and past anxiety and depressive disorders and to the harm avoidance dimension of the Tridimensional Personality Questioinnaire (TPQ), the predecessor of the TCI (Russo et al. 1994). In a study of patients with comorbid somatization and panic disorders, such patients had significantly higher novelty seeking values than both the patients with panic only and the control subjects. The only significant correlation in the study was between the number of symptoms of somatization disorder and novelty seeking assessed with TPQ (Battgalia et al. 1998). In an epidemiological setting Karvonen et al. were able to detect from the whole sample an association between somatization and high harm avoidance and reward dependence (Karvonen et al. 2006). Initially, Cloninger's theory was that a temperament pattern of high NS and low HA would lead to chronic somatic anxiety (Cloninger 1986).

Garyfallos et al. suggested that histrionic and dependent personality disorders (PD) differentiated the somatoform disorders best from the control group. Comorbid personality disorder in somatoform disorder manifested more severe overall psychopathology and deteriorated functioning (Garyfallos et al. 1999). Stern et al.

reported the prevalence of personality disorders among patients with somatisation disorder to be 72% compared with 36% among controls. Certain personality disorders, including passive-dependent, histrionic, and sensitive-aggressive, occurred significantly more commonly in the SD patients than controls (Stern et al. 1993). PD comorbidity in SD patients was 62.9%, compared to 28.2% in controls according to Garcia-Campayo et al. The common PDs were paranoid, obsessive–compulsive, and histrionic in SD patients, as compared with controls (Garcia-Campayo et al. 2007).

2.3.4 Biological findings

The biological basis for severe somatization is largely unknown. In this chapter the biological findings of severe somatization and syndromes resembling it are reviewed. Several observations with different assessment methods have been done in severe somatization.

Evoked response potential finding has been reported and interpreted as a disturbed capacity to filter afferent stimuli (Gordon et al. 1986, James et al. 1990). In one study, the psychophysiological reactivity was assessed during relaxation and mental distress - 24 patients with somatization syndrome, 34 patients with somatization syndrome and comorbid major depression, and 23 healthy controls (Rief and Auer 2001). As mental stressor, the span of apprehension test, which requires continuous attentional processing, was used. This is a choice-reaction time task with visual stimuli including differing numbers of distracting elements. For most physiological signals included in this study (such as muscular reactivity, electrodermal responses, peripheral circulation), no significant differences between healthy controls and patients with somatization syndrome were found. In healthy controls, the change from attention tasks to rest periods was associated with a substantial decrease in heart rate activity ("recovery response"). This reduction of physiological activity after mentally distressing tasks was not found in patients with somatization syndrome. This effect was not attributed to the occurrence of depression or anxiety. This raised an idea of habituation disturbance in somatization (Rief and Auer 2001).

There is a finding that distressed patients with "unexplained" physical symptoms show a tendency for hypocortisolism (Heim et al. 2000). Other studies have found normal or even increased concentrations of free cortisol when controlled for depression. (Rief et al. 1998, Rief and Auer 2000).

An Immunology study differentiated somatization from depression and healthy controls by showing higher endogenous cytokine of Clara cell protein (CC16) scores as well as lower serum interleukin (IL)-6 values in somatization syndrome compared to other groups (Rief et al. 2001). Activation of the immune system seems to induce behavior patterns that are similar to the illness behavior seen in depression and somatization (Rief and Barsky 2005).

Reduced blood tryptophan levels with somatoform symptoms observed in non-depressed patients suggests a possible monoaminoergic transmitter system alteration,

and furthermore, development of functional somatic symptoms in general (Rief et al. 2004a).

The SPECT study of somatization disorder patients showed hypoperfusion in different brain areas in seven out of 11 subjects (Garcia-Campayo et al. 2001). However, the observations were heterogenic in nature.

Decreased regional blood flow, assessed with SPECT, in the thalamus and basal ganglia contralateral to the sensorymotor deficit has been described in six female and one male suffering from conversion (Vuilleumier et al. 2001). The hypoactivation resolved after clinical recovery and the results suggest that hysterical conversion may entail a functional disorder in striatothalamocortical circuits controlling sensorimotor function and voluntary motor behavior (Vuilleumier et al. 2001).

Yazici and Kostakoglu assessed cerebral blood flow changes in five patients with conversion disorder (Yazici and Kostakoglu 1998). They made observations of temporal and parietal perfusion defects in the dominant hemisphere using SPECT technique. Only one patient was noted to have a right-sided temporal perfusion defect in addition to a left-sided temporal defect. They indicated the right-sided perfusion defect was associated with the symptom of paresis in his left leg, which persisted during imaging (Yazici and Kostakoglu 1998). Tiihonen et al. (1995) reported a case with left-sided paralysis and paresthesia associated with mild aphatic symptoms. Prior to recovery, there was increased perfusion in the right frontal lobe (+7.2% compared with the left side) and hypoperfusion in the right parietal region (-7.5% compared with the left side). These results suggest that psychogenic paresthesia may be associated with the simultaneous activation of frontal inhibitory areas and inhibition of the somatosensory cortex. It seems that distressing psychological events may alter the neurophysiology of the human brain in a specific way and trigger symptoms such as amnesia or paresthesia through activating or inhibiting critical areas of the brain (Tiihonen et al. 1995).

A number of conditions are common in the clinical environment for which no readily demonstrable pathologies exist to explain the symptoms that plague affected individuals. These so called medically unexplained syndromes or functional somatic syndromes include entities such as fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, multiple chemical sensitivity and chronic low back pain and they resemble somatization disorder and undifferentiated somatoform disorder. The symptoms of the different syndromes are overlapping with each other and the approach is commonly based on medical specialty (Wessely et al. 1999). Brain imaging studies have been done in these groups in order to clarify the possible pathology of the conditions.

Fibromyalgia

Fibromyalgia is a syndrome whose main features include chronic, widespread musculoskeletal pain and stiffness in association with fatigue and poor sleep. Fibromyalgia patients may also experience a variety of other symptoms, including emotional distress, depression, decreased motivation, and dyscognition. The American

College of Rheumatology (ARC) criteria for the diagnosis of fibromyalgia consist of pain in all four body quadrants in combination with excess tenderness to manual palpation of at least 11 of 18 muscle-tendon sites, in the absence of a clinically demonstrable peripheral nociceptive cause (Wolfe et al. 1990).

Brain imaging studies of fibromyalgia that measured regional cerebral blood flow (rCBF) at rest using positron emission tomography (PET) or single photon emission computed tomography (SPECT) have shown hypoperfusion in various brain regions of fibromyalgia patients compared to controls (Williams and Gracely 2006). Mountz et al. used SPECT to evaluate baseline levels of rCBF in ten female patients with fibromyalgia and in seven healthy female control subjects. Results from this early study suggested that patients with FM had lower rCBF (that is, lower neural activity) than healthy control subjects during a quiescent resting state. Reduced neural activity was found both in the right and left thalamus and in the right and left caudate nucleus (Mountz et al. 1995). Kwiatek used SPECT to assess resting rCBF in 17 patients with FM and in 22 healthy control subjects. These investigators observed decreased rCBF in the right thalamus, the inferior pontine tegementum and near the right lentiform nucleus but, unlike the initial study, no decreases in either the left thalamus or in the caudate nuclei were noted (Kwiatek et al. 2000). The consistent finding of reduced rCBF in the right thalamus was also observed in a study by the group, who examined the influence of historical factors on the SPECT results. This group divided the sample of patients with fibromyalgia into those with a traumatic etiology (n = 11) and those with a more gradual onset (n = 21). Both patient groups, compared to 29 healthy controls, showed significantly decreased rCBF in the left and right thalamus. However, only patients with a gradual atraumatic etiology showed reduced rCBF in the left and right caudate (Bradley et al. 1999).

One fMRI study of patients with FM applied blunt pressure to the left thumbnail bed of 16 right-handed patients with FM and 16 right-handed matched controls. Each FM patient underwent fMRI while moderately painful pressure was being applied. The functional activation patterns in FM patients were compared with patterns in normal controls. The results show that equal perceived pain intensity (achieved with significantly less pressure in the patients than controls), produced similar increases in neural activity in a network of brain structures implicated in pain processing. These increases were observed in structures involved in sensory discriminative processing (contralateral SI, SII), sensory association (contralateral superior temporal gyrus, inferior parietal lobule), motor responses (contralateral putamen and ipsilateral cerebellum) and affective processing (contralateral insula). Patients and controls also shared a similar region of decreased neural activation in the ipsilateral SI. In contrast to the extensive common activations observed in both patients and controls when subjective pain perception was equated, there were no common activations when the actual pressure stimulus intensity was equated. Applying a low stimulus pressure to both healthy controls and FM patients resulted in 13 regions showing statistically greater activation for patients (that is, contralateral SI, inferior parietal lobule, insula, ACC and posterior cingulate cortex; ipsilateral SII cortex; bilateral superior temporal gyrus, and cerebellum) whereas only one region (ipsilateral medial frontal gyrus)

demonstrated greater activation in controls. These results also suggested that the brain activations in patients and controls are consistent with their verbal reports of pain magnitude. Additionally, these results demonstrated that, in the caudate nucleus and the thalamus, patients with FM showed reduced activation in comparison to controls (Gracely et al. 2002). Another fMRI study suggested different response to non-painful warm stimuli - FM subjects had significantly greater activity than controls in prefrontal, supplemental motor, insular, and anterior cingulate cortices. Additionally, in response to painful stimuli, FM subjects had greater activity in the contralateral insular cortex (Cook et al. 2004).

Two PET competitive binding studies using the D2/D3 receptor antagonist [11C] raclopride showed that more striatal dopamine is released in response to tonic noxious muscle stimulation in healthy human subjects compared to non-painful stimulation (Scott et al. 2006, Wood et al. 2007). In contrast, the dopamine response of fibromyalgia patients did not differ between painful and nonpainful muscle stimulation (Wood et al. 2007).

Cerebrospinal fluid concentrations of endogenous opioids have been found to be elevated in FM, suggesting a disturbance also of this neurotransmitter system (Baraniuk et al. 2004). Harris et al. performed a PET study investigating the relationship between alterations in the cerebral opioidergic system and pain in fibromyalgia. At rest, patients showed decreased binding potentials for the exogenously administered μ-opioid receptor agonist carfentanil in several brain areas, including the ventral striatum, the anterior cingulate cortex, and the amygdale (Harris et al. 2007). The posterior cingulate cortex is the only brain region in which resting rCBF has been found to be increased in patients with fibromyalgia (Wik et al. 2003). In line with this, activation in this area is decreased when exogenous pain is administered (Wik et al. 2006).

There is a structural study reporting decreased gray matter density in the thalamus of fibromyalgia patients (Schmidt-Wilcke et al. 2007). Another analysis compared brain gray matter density in fibromyalgia patients and healthy controls (Kuchinad et al. 2007).

Two studies have examined gray matter density in fibromyalgia patients (Kuchinad et al. 2007, Schmidt-Wilcke et al. 2007). Kuchinad and others showed that total gray matter volume was less in fibromyalgia patients than in healthy controls, with patients showing a 3.3 times greater age-associated decrease in gray matter than healthy controls. Regional gray matter density analyses revealed gray matter loss in regions associated with pain modulation or stress, such as the cingulate, insular and medial frontal cortices, parahippocampal gyri, and thalamus. Schmidt-Wilcke and colleagues also found gray matter increases in the striatum bilaterally and cerebellum (Kuchinad et al. 2007, Schmidt-Wilcke et al. 2007).

Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a complex and medically unexplained illness that is characterized by severe and prolonged disabling fatigue and a combination of

symptoms, including sleep disturbance, musculoskeletal pain and impairment in concentration and short-term memory (Fukuda et al. 1994). Fatigue is the central symptom of CFS and emphasizes the role of the central nervous system in the subjective perception of fatigue (Georgiades et al. 2003, Kent-Braun et al. 1993). CNS factors such as emotion, attention and motivation can all be involved in fatigue perception (St Clair Gibson et al. 2003).

Functional neuroimaging, especially single photon emission computed tomography (SPECT) of regional cerebral blood flow, has been used to assess specific patterns of blood flow alteration in patients with CFS, but conflicting results have been obtained. Although most studies describe lowered regional cerebral blood flow in a variety of brain regions (mainly frontal and temporal), no consistency of findings can be observed across studies (Mayberg 1995).

A positron emission tomography (PET) study by Tirelli et al. examined cerebral glucose metabolism using [18F]FDG and a region of interest (ROI) based approach for data analysis. These investigators found significant hypometabolism compared with normal controls in the right mediofrontal cortex and the brain stem. They also compared CFS with depression and found hypometabolism bilaterally in the upper frontal regions in the latter (Tirelli et al. 1998). Siessmeier et al. performed another [18F]FDG-PET trial with 26 patients (13 female, 13 male). After stereotactic normalization, single subject comparisons with an age and sex matched normal database (n = 18) and a group comparison between the patients and normal controls were undertaken. 12 of the 26 patients showed no significant decrease in FDG uptake compared with the controls. Of the remaining 14, 12 showed hypometabolism bilaterally in the cingulate gyrus and the adjacent mesial cortical areas and no specific pattern for CFS could be identified (Siessmeier et al. 2003).

In fMRI studies there have been comparisons of brain responses to cognitively challenging tasks between CFS patients and healthy controls (Caseras et al. 2006, Caseras et al. 2008, Cook et al. 2007, Lange et al. 2005) but only two of these studies correlated subjective fatigue scores with brain activity during a working memory task (Caseras et al. 2008, Cook et al. 2007). Significant positive relationships were found for cerebellar, temporal, cingulate and frontal regions and a significant negative relationship was found for the left posterior parietal cortex (Cook et al. 2007). During the provocation of fatigue, CFS patients reported feelings of both fatigue and anxiety and, compared to controls, they showed increased activation in the occipito-parietal cortex, posterior cingulate gyrus and parahippocampal gyrus, and decreased activation in dorsolateral and dorsomedial prefrontal cortices (Caseras et al. 2008). In the study of the patients with CFS, there was a greater activation than in control subjects in medial prefrontal regions, including the rostral anterior cingulate gyrus, during the lower load condition. The second finding of this study was that the CFS group showed reduced activation in dorsolateral prefrontal and parietal cortices during the more demanding levels of the task (Caseras et al. 2006). An observation of an earlier fMRI study showed that the ventral anterior cingulate cortex was active when healthy controls made an error, but remained inactive when CFS patients made an error (de Lange et al. 2004).

Several structural (Buchwald et al. 1992, Cope and David 1996, Lange et al. 1999, Natelson et al. 1993, Schwartz et al. 1994a,b) neuroimaging studies have investigated possible cerebral correlates of CFS. Studies of brain morphology in CFS have focused on (subcortical) white matter abnormalities, which manifest themselves as foci of bright intensity on T2-weighted MR scans. These studies provide conflicting evidence for cerebral abnormalities. Whereas some studies report an increased number of subcortical white matter abnormalities associated with CFS (Buchwald et al. 1992, Lange et al. 1999, Natelson et al. 1993, Schwartz et al. 1994a), other studies observed equal numbers of white matter abnormalities in healthy volunteers and CFS patients (Cope et al. 1995, Cope and David 1996). In voxel-based morphometric studies one study observed significant reductions in global gray matter volume in both cohorts of CFS patients, as compared to matched control participants, but did not detect regionally specific difference in grey matter (GM) (over and above global GM differences). The finding was interpreted that the observed GM reduction in the CFS patient groups is a global rather than a local phenomenon (de Lange et al. 2005). Another study found that patients with chronic fatigue syndrome had reduced gray-matter volume in the bilateral prefrontal cortex. Within these areas, the volume reduction in the right prefrontal cortex paralleled the severity of the fatigue of the subjects (Okada et al. 2004).

Many different functional syndromes have been described. In fact, each medical specialty seems to have at least one: for rheumatologists, prominent muscle pain and tenderness is fibromyalgia; for gastroenterologists, abdominal pain with altered bowel habit is irritable bowel syndrome; for infectious-disease specialists, chronic fatigue and myalgia is chronic (postviral) fatigue syndrome; for allergologists hypersensitivity is named multiple chemical sensitivity (or idiopathic environmental intolerance (IEI); for gynecologists unclear pain symptoms fall into the category of chronic pelvic pain; for ear, nose and throat specialists, lump in throat is globus syndrome; for cardiologists unclear origin of chest pain is named atypical chest pain; and for dentists temporomandibular joint dysfunction or atypical facial pain as well as burning mouth covers functional somatic symptoms (Wessely et al. 1999).

There is growing empirical evidence of a link between functional somatic syndromes and altered functioning of the central nervous system. This has gradually replaced suggested abnormalities located in specific organ systems. For example, muscle dysfunction was originally suggested as the basis of chronic fatigue syndrome or/and fibromyalgia, however the explanation has been largely replaced by an appreciation of the role of central and neuroendocrine mechanisms (see above). Additionally, indirect evidence of abnormalities in serotonergic central-nervous-system pathways has also been presented for several disorders, including non-nuclear dyspepsia, irritable bowel syndrome, chronic fatigue syndrome, and premenstrual syndrome (Wessely et al. 1999).

2.4 CONCLUSION OF THE LITERATURE REVIEW

In general, the possible CNS pathophysiology of these medically unexplained syndromes is investigated in FM and CFS, but not in somatization disorder. In somatization disorder and undifferentiated domatoform disorder there is a body of literature of epidemiology, psychology, clinical features and comorbidities but less of pathophysiology. Reports of PET, SPECT and MRI in somatization disorder and undifferentiated somatoform disorder are uncommon and lacking control groups. However, the existing representavive case reports indicate CNS pathology involvement. Further investigation of an association with possible CNS pathology and somatization disorder and undifferentiated somatoform disorder is warranted.

3. AIMS OF THE PRESENT STUDY

The general aim of this thesis is to explore the CNS pathology of subjects who were suffering from medically unexplained symptoms and classified as suffering from somatization disorder or undifferentiated somatoform disorder according to DSM-IV criteria. Comparison groups were healthy volunteers without illness history. The specific goals of individual publications are listed below.

Aim		**Publication**
1.	To explore possible central nervous system disturbances in glucose metabolism in severely somatizing women	I
2.	To investigate the brain morphology in severely somatizing women	II
3.	To study temperamental factors and brain regional glucose metabolism and their association with severe somatization	III
4.	To report a case of medically unexplained hemisyndrome classified under diagnosis of somatization disorder	IV

4. MATERIAL AND METHODS

4.1 SUBJECTS AND CONTROLS

The patients were recruited for each of the studies through health care units in the area of Turku University Central Hospital - two hospital district areas (Varsinais-Suomi and Satakunta). Patients were recruited to the studies if they had persistent, medically unexplained symptoms (MUS) or a previously established diagnosis of somatization disorder or undifferentiated somatoform disorder. Healthy volunteers were controls. They were subjects with a good state of health with neither known illness nor requirement for regular medication. The examination of their current state of health was done by questioning.

In total 15 female and 10 male patients gave informed consent (IC). Five female and three male subjects were excluded during the screening phases. 10 female and seven male were included and completed the study protocol requirements. The seven male patients are not yet analyzed as group. One of the seven male subjects is reported as case report.

12 of the female controls were recruited via different sources and all the assessments defined in the protocol were applied to them. Five female control subjects were recruited from the PET Center pooled control database. Eight male control subjects were recruited via different sources and all the assessments defined in the protocol were applied to them, correspondingly. Six male control subjects were recruited via the PET center control database. Five male controls were used in study IV.

4.2 STUDY DESIGN

The study design was approved by the Ethics Committee of the Turku University, Turku University Hospital and Turku City Hospital. An open, non-randomized, control-group trial design was applied to all settings.

In Study I, [18F]-FDG cerebral metabolic rate was assessed in severely somatizing women (n = 10) and compared to healthy controls (n = 17).

In Study II, brain structures of severly somatizing women (n = 10) was assessed with MRI and compared with those from healthy volunteers (n = 16).

In Study III, association of temperament and brain metabolism with severe somatization in women were assessed using logistic regression (patient n = 10, control n = 12).

In study IV, a male patient with severe somatization and left-side symptom gradient was compared to age and gender matched healthy controls (n = 5).

4.3 CLINICAL ASSESSMENT

Somatization disorder or undifferentiated somatoform disorder as a clinical diagnosis consists of a description of symptoms as defined in DSM-IV. The classification includes at least 8 symptoms in different body organ systems with duration of at least two years and, in somatization syndrome, with the onset age below 30 years. Essential is the exclusion of other possible reasons causing the symptoms and clinical evaluation of the impact of the findings made in relation to the clinical picture of the patient.

4.3.1 Three-phase procedure for patient selection and diagnosing

Informed written consent according to the Declaration of Helsinki was obtained from each subject before enetering the study. The investigation had the approval of the ethics committees of Turku University, Turku University Central Hospital and Turku City Hospital.

The diagnostic procedure (case selection) consisted of three-phase auditing. The potential cases were interviewed by a psychiatric resident, who elicited the basic information about the patient's personal and illness history, symptoms, symptom attribution, social context and diagnostic procedures, and the treatments previously or currently given. The patients' medical records were also reviewed for diagnostic purposes. All patients with a history of neurological or systemic illness were excluded as well as patients over 60 years of age. A diagnosis of somatization disorder or undifferentiated somatoform disorder was made if indicated.

A research psychiatrist audited the first phase results by interviewing the patient and confirmed or rejected the diagnosis of somatization or undifferentiated somatoform disorder.

The third phase was the validation of the diagnosis. Two psychiatrists independently diagnosed the patients based on written information collected about the patients. Only the patients who received a diagnosis of somatization disorder or undifferentiated somatization disorder from both investigators in this blind selection were accepted.

4.3.2 Symptom Checklist – SCL-90

In order to evaluate the spectrum of symptoms and "filter" those with a prominent somatization dimension as well as verifying the absence of comorbid axis I, the SCL-90 was chosen as additive tool in the evaluation of the patients. Initially SCL-90 was introduced by Derogatis et al. (1973). SCL-90 is a symptom questionnaire consisting of nine subscales covering following dimensions: somatization, obsessive-compulsivness, anxiety, interpersonal sensitivity, depression, hostility, phobic anxiety, paranoid ideation, and psychotism, may be useful in a research setting as an instrument for measuring the change in symptomatic distress, or as a screening instrument. It is validated in Finnish population (Holi et al. 1998).

4.4 EMISSION TOMOGRAPHY

Nuclear medicine is applying and integrating methods from medicine, radiochemistry and medical physics. Clinical diagnosis, therapy and scientific research are the main applications of nuclear chemistry. Functional imaging of the human brain are performed using emission tomography methods such as PET and single photon emission (computed) tomography (SPET or SPECT).

4.4.1 PET principles

PET is a non-invasive imaging method. It enables functional imaging of different physiological and biological events *in vivo* in the target tissue. It can be used to quantitatively measure cerebral blood flow, cerebral glucose metabolism or brain neurotransmitter system function. The methodology of PET is based on positron imaging isotopes, which are artificially manufactured – most often in cyclotron. The isotopes' applicability in PET studies is based on their relatively short half-lives (T1/2). The most common isotopes are oxygen-15 (15O; T1/2 = 2 min), carbon-11 (11C; T1/2 = 20 min), and fluorine-18 (18F, T1/2 = 110 min). Numerous biological substrates can be labeled to achieve a PET tracer. The labeling usually does not significantly alter the physiological characteristics of the labeled molecule.

A positron is a β-particle which possesses the same mass and magnitude of electrical charge and expresses similar behavior as an electron. Positron is positively charged, whereas the electron is negatively charged. As a consequence, positron is an antimatter particle of an electron. As a result of radioactive decay a positron is emitted from a nucleus and it travels a variable distance before it encounters an electron. This distance correlates with the kinetic energy of the positron, which is dependent on the radionuclide. For example, the average energy of positrons originated from the decay of an 11C isotope is 0.386 MeV and the average distance they travel is 0.56 mm (Bacharach 1992). When a positron and an electron are interacting, a phenomenon called annihilation will occur. In annihilation, the masses of an electron and positron will be converted into two γ rays possessing energy 511 keV each and traveling in almost exactly opposite directions (180° ± 0.25°, Figure 2) (Bacharach 1992).

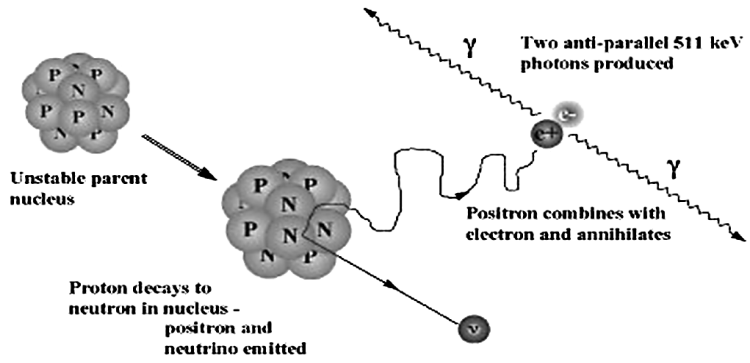

Figure 2. Annihilation, two γ-rays of 511keV energy.

PET scanning technique is based on the coincidental detection of two γ rays on the opposite sides of the PET scanner's detection ring (i.e. gantry, Figure 3). These coincidences reveal the annihilation happened somewhere along the imaginary line connecting the two detectors (Figure 3). As other positrons originating from the same source are annihilated, additional coincidences help to locate the source. PET scanning views the target from multiple angles and radioactivity, measured from each angle in each acquisition plane, can be collected into the sinogram. The sinogram contains the information needed for the reconstruction of the three-dimensional (3D) PET image. In addition, information can be collected in multiple time frames which are combined during image analysis.

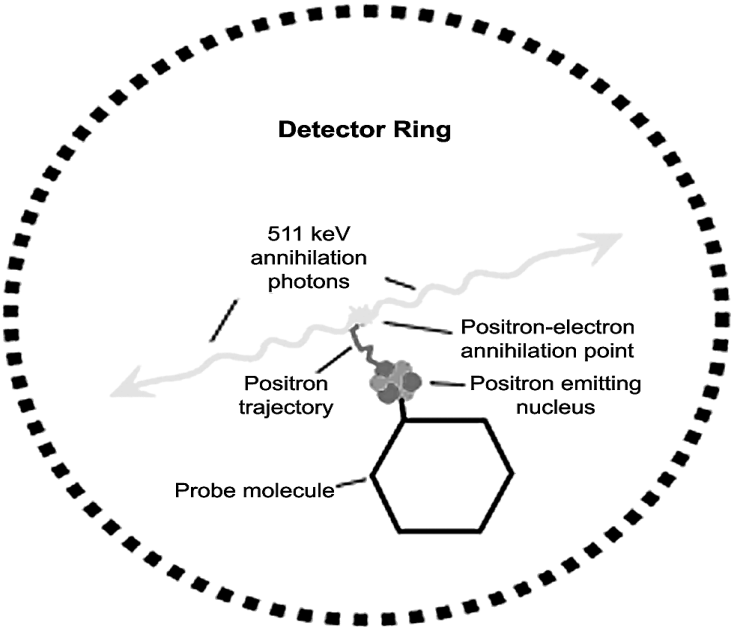

Figure 3. PET scanner technique, detection ring.

The accuracy of a PET scanner to detect the location of the annihilation depends on the spatial resolution of the scanner. This resolution can be improved by increasing the number of scintillation crystals on the detector ring of the scanner or by decreasing the physical distance between the detector pairs. If there is neither scatter nor statistical noise present, the best resolution of the scanner can be defined as the in-plane resolution. Full-width-at-half-maximum (FWHM) is usually describing the resolution at which objects closer than 1 FWHM cannot be separated. The ultimate spatial resolution of PET images is dependent on the distance that the positron travels before annihilation as well as non-collinearity of the annihilation photons meaning that due to scatter, the angle of the two photon trajectories will not be exactly 180°.

Not all annihilation events are detected by the PET scanner. This is the result of dead-time and the sensitivity of the scanner. The dead time of the scanner is the time period lost in signal processing. The sensitivity of the scanner defines the proportion of the

occurred annihilations of a known radioactive source which are detected by the scanner. The scanner sensitivity can be improved by removing the septa between the detector rings of the scanner (i.e. scanning in 3D mode). The 3D mode allows more scatter than the 2D mode (Accorsi et al. 2004), but the increased scatter can be corrected with different kinds of scatter correction algorithms.

Images must also be corrected for random coincidences and photon attenuation. Random coincidences occur when two γ rays from different annihilations are interpreted as originating from the same annihilation. The correction from these randoms can be done, for example, by. estimating the rate of single hits and subtracting them from the coincidence data before image reconstruction. Attenuation of γ rays by subject's own tissues can be corrected with a separate attenuation correction scan, i.e. a transmission scan, performed with, e.g. extra-corporeal 68Ge (positron emitting Germanium-68) rod-sources.

PET is widely utilized nowadays in areas of scientific research including brain research, pharmacology, oncology, internal medicine, pain medicine, surgery and physiology. The areas of neurology and oncology are increasingly utilizing PET as a diagnostic tool. Principally any compound could be labeled with a positron isotope and therefore it is used in the development of new drugs. PET can be applied to determinate the distribution and/or, mechanism of action of a novel drug (Otte and Halsband 2006). Further development includes the PET-CT-scanner combining functional imaging with precise anatomic reference (Otte and Halsband 2006).

4.4.2 SPECT principles

The use of gamma-emitting isotopes is the basis of SPECT. The SPECT camera is a gamma-camera which detects single photons instead of coincidence pairs. The detector heads of the gamma-camera are planar, and they can be moved around the subject. Technetium-99m (Tc-99m) is the most commonly used isotope and its half-life of 6 hours enables longer tracer accumulation times than most PET tracers (Jaszczak and Tsui 1995). With an appropriate choice of isotopes with characteristic photon energy, SPECT has the advantage of imaging two tracers at the same time, which is not possible with PET. multiple-headed gamma-cameras have improved the sensitivity of the SPECT. Two-headed gamma-cameras can also be used for coincidence imaging ("dual-head PET"). SPECT advantages include lower costs, feasibility, and commercially available isotopes, which do not require an on-site cyclotron.

4.4.3 Image acquisition and processing

The PET studies were performed using an 18-ring GE Advance whole body – tomograph (General Electric Medical Systems, Milwaukee, WI, USA). The GE Advance scanner has an axial resolution of 4.3 mm and a spatial resolution of 4.3 mm (DeGrado et al. 1994). Before emission scan, an 8 min transmission scan for correction of photon attenuation was performed with a pair of pin sources containing 68Ge/68Ga. All data were corrected for decay, dead time and photon attenuation. Dynamic scans

were reconstructed pixel by pixel into a 128x128 matrix. A head holder was used for fixation of the head.

[18F]FDG synthesis was a slightly modified version of the method reported by Hamacher et al. (Hamacher et al. 1986). The radiochemical purity exceeded 99%. 5 ml of a solution with a dose of about 3.7 MBq/kg of [18F]FDG was injected intravenously over one minute and a dynamic scan for 50 min (10 x 300 sec frames) was acquired. Altogether 21 blood samples for measurement of plasma radioactivity were withdrawn and the radioactivity was measured with an automatic gamma counter (Wizard 1480 3", Wallac, Turku, Finland).

4.4.4 Quantification of brain metabolism

A three-compartmental model of [18F]FDG kinetics was used (Phelps et al. 1979) in studies I and III. Plasma and tissue activity curves were analyzed graphically to calculate a rate of constant (Ki) for the fractional rate of tracer transporter and phosphorylation (Patlak and Plasberg 1985). The rCMRGlc (regional cerebral metabolic rate of glucose) was obtained as follows:

RCMRGlc = Ki x (Glc)p / LC

Where (Glc)p denotes the average plasma glucose concentration during the acquisition, and LC denotes the lumped constant which corrects for differences in the transport and phosphorylation of [18F]FDG and glucose. The LC value used was 0.81 (Hasselbalch et al. 1998).

4.4.5 ROI – based analysis

The Investigator selects and defines the regions of interest (ROIs) for PET data analysis. To be able to localize different brain regions anatomically, MRI is needed. After the dynamic PET image is reconstructed, the MRI image is combined with the PET image. ROIs are drawn manually on MRI slices following the anatomical landmarks, and imported onto the PET images. Time-activity curve is calculated for each ROI and a model that has been validated for the tracer is fitted to the observed data. This method enables quantitative comparisons in tracer binding between different subjects or experimental conditions on an individual or a group level. Minor differences on group level may be missed due to inter-individual variability of cerebral metabolic rate of glucose. Additionally, differences in tracer uptake in the subregions of a ROI or regions outside the ROIs may not be detected.

4.5 MAGNETIC RESONANCE IMAGING

4.5.1 MRI principles

MRI is an application of nuclear magnetic resonance (NMR), a well known analytical method of chemistry, physics and molecular structural biology. MRI is used as a

technique for producing anatomical images, but it also gives information on the physical-chemical state of tissues, flow diffusion and motion information (functional MRI, fMRI).

Most elements have at least one reasonably abundant isotope whose nucleus is magnetic. In biological materials, the magnetic nuclei of 1H, 13C, 23Na, 31P, and 39K are all abundant. The hydrogen nucleus (a single proton) is abundant in the body due to high water content of non-bony tissues. When the body is immersed in a static magnetic field, slightly more protons become aligned with the magnetic field than against the static field. At 0.25T (2500 gauss) and 25°C the difference between these aligned populations of about one proton in a million produces a net magnetization. A rapidly alternating magnetic field at an appropriate resonant frequency in the radio frequency (RF) range, applied by a coil near the subject in the static magnetic field, changes the orientation of the nuclear spins relative to the direction of the static magnetic field. These changes are accompanied by the absorption of energy (from the alternating magnetic field) by nuclei which undergo the transition from a lower energy state to higher one. When the alternating field is turned off, the nuclei return to the equilibrium state, emitting energy at the same frequency previously absorbed. The nuclei of different elements, and even of different isotopes of the same element, have very different resonance frequencies. For a field of 0.1T (1000 gauss), the resonance frequency of protons is 4.2 MHz and that of phosphorus is 1.7 MHz. Thus, the magnetic nuclei in the body, when placed in a static magnetic field, can be thought of as tuned receivers and transmitters of RF energy.

The principal components of the MRI machine are the magnetic radiofrequency (rf) coils and the gradient coils. Magnet types in current use are of the superconductive, resistive and permanent magnet designs ranging in strength from 0.08 to 4 T and further (T = 10000 gauss). The majority of MR systems use superconductive magnets which provide fields of high strength and stability.

4.5.2 Image acquisition and processing

In study II, subjects underwent MRI studies of the brain as a part of the project protocol. A commercial 1.5 T MR imager (Siemens Magnetom, Erlangen, Germany) with a standard head coil was used. In all cases, sagittal three-dimensional MPR (magnetization prepared rapid gradient echo; TR 10, TE 4, flip angle 10°, matrix 192x256, contigious 1.5 mm slices, 1 acquisition) were obtained.

For volume measurements, 3 mm thick slices were reconstructed. Volume measurements were performed on standard work console by manually outlining the structures defined as ROIs. Successive slice areas were summed and multiplied by the slice thickness. Identifiable anatomical structures were used in demarcation of the structures under investigation.

Additional measurements were performed in order to exclude interindividual size variability. Intracranial coronal area was measured at the level of the commissural anterior; and this area was used to normalize the volumes with respect to head size (by

multiplying the volumes by 100 and dividing by intracranial area). The intra-rater reliability procedure was performed to test the method reproducibility. Measures were performed by the rater without knowledge of the clinical data and diagnostic category of the patients.

4.6 TEMPERAMENT AND CHARACTER INVENTORY

Cloninger introduced a seven-factor personality model: The Temperament and Character Inventory (TCI) consisting of four largely independent and stable factors of temperament and three factors for character. The temperament factors are novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence (PS), the character factors are self-directedness (SD), co-operativeness (CO), self-trancendence (ST), correspondingly. Temperament traits are thought to be moderately heritable. (Svrakic et al. 1993, Cloninger et al. 1994). TCI was developed from Tridimensional Personality Questionnaire (TPQ) (Russo et al. 1994).

NS is defined as tendency to react actively to novel stimuli, cues to potential rewards or relief of punishment. HA is a tendency to respond intensively to signals of aversive stimuli, thus resulting to inhibition or stop of the behavior. RD is defined as active response to reward signals, especially related to social ones, thereby maintaining and continuing particular behaviors. PS is the tendency to persevere behavior despite frustration and fatique (Cloninger et al. 1993, Cloninger et al. 1994, Miettunen et al. 2004).

The assessment of temperament profiles was obtained with the Finnish version of the 240-item TCI (Cloninger 1986, Cloninger 1987, Cloninger et al. 1993, Cloninger et al. 1994). The psychometric properties of the Finnish scale have been shown to be satisfactory (Miettunen et al. 2004).

The TCI was obtained from every study subject entering the study according to the protocol. TCI was not obtained from PET Centre pooled healthy volunteer dataset.

4.7 STATISTICAL ANALYSIS

In studies I and II the Student's t-test of paired samples was used to test the differences in the parameters of interest, rCMRGluc of ROIs and volumes of defined brain structures, between the groups.

In study III a logistic regression model was used to determine the phenomena explaining somatization. Temperament factors and predefined glucose metabolism regions were continuous independent variables explaining somatization.

In study IV the case was compared to a group of healthy volunteers. The difference was defined as a magnitude of standard deviation difference between mean rCMRGluc for the patient and the control groups.

In studies I – III the statistical analyses, a two-sided value of $P < 0.05$, was considered statistically significant. Data is presented as mean ± SD unless otherwise stated. In study IV a difference of SD ≥ 2 of the mean asymmetry of the control subjects was considered abnormal and of clinical value.

Statistical analyses were made using SPSS (Statistical Package for the Social Sciences, version 7.5 and version 9.0, SPSS Inc., Chigago, IL, USA) and SAS (Statistical Analysis System, version 8.02; SAS Institute Inc., Cary, NC, USA)

5. RESULTS

5.1 REGIONAL CEREBRAL METABOLIC RATE OF GLUCOSE IN SEVERELY SOMATIZING WOMEN (I)

Ten female cases of somatization disorder (n=6) or undifferentiated somatoform disorder (n=4), without current psychiatric comorbidities according to the DSM-IV criteria, were identified. Their brain glucose metabolism, measured with [18F]FDG uptake using PET methodology, was compared to 17 healthy female volunteers. In this exploratory study an average of 240 ROIs per case, covering 28 areas of brain bilaterally (14 unilateral areas), were drawn and analyzed (Table 3 in the study I). Four areas of cerebral hypometabolism ($P < 0.05$) were detected, namely both caudate nuclei, left putamen and right precentral gyrus. A tendency of diffuse wide-range hypometabolism along the frontal cortex, putamen as well as thalamus ($P < 0.2$) was also observed. No hypermetabolic areas were detected. Additionally, global cerebral and cerebellar glucose metabolism was investigated and no statistical difference was seen. There were also no focal abnormalities in the MRI scans of the patients that could explain the hypometabolism.

5.2 MAGNETIC RESONANCE IMAGING IN WOMEN WITH SEVERE SOMATIZATION (II)

Based on the findings from study I it was chosen to evaluate bilaterally the two brain structures of severely somatizing women, namely nuclei putamen, caudate. Hippocampal area bilaterally was chosen as we wanted to investigate whether threre are similar changes to be found as seen in major depressive disorder (MDD). The same 10 female patients as in study I and 16 healthy volunteers participated in study II. All study subjects underwent a brain MRI examination and assessment of the volume of the structures as a part of the study protocol. The scan was performed with a 1.5 T instrument. A standard work console was used in manual outlining of the structures. Volume measurement was done blinded to study subject's clinical state and possible diagnosis.

In the main analysis both right and left caudate nucleus were enlarged compared to healthy controls ($P < 0.05$). The supplementary analysis was performed in a way where individual intracranial size variability had been taken into account by measuring the intracranial coronal area. This value was used to normalize the volumes with respect to head size. Also this method indicated a statistically significant enlargement of the caudate nuclei, but also a reduction of left hippocampal area ($P < 0.05$).

5.3 ASSOCIATION OF TEMPERAMENT AND BRAIN METABOLIC FACTORS WITH SOMATIZATION (III)

The association of temperament profiles and brain metabolism with severe somatization were examined in study III. TCI was obtained from 12 female control subjects and they were included in the analysis with the 10 female patients in studies I and II. TCI was obtained from every study subjects as part of the protocol examination procedure. In a univariate logistic regression model low novelty seeking and high harm-avoidance as temperament traits as well as reduced rCMRGluc in putamen and caudate nuclei seemed to be associated with severe somatization ($P < 0.05$, Table 4 in the study). In a stepwise logistic regression model reduction in metabolism of caudate nuclei was statistically significant ($P < 0.05$) and low novelty-seeking almost reached statistical significance ($p = 0.068$).

5.4 PATHOPHYSIOLOGY OF HEMISYNDROME – A CASE REPORT (IV)

Study IV examined the pathophysiology of the hemisyndrome using [18F]FDG-PET in a 54-year old man. Continuous symptoms with left-side gradient of the body without objective findings in routine neurological examination and follow-up, indicated additional procedures and the patient was included in the investigational program according to the protocol. In the PET-image there were obvious visible pattern of metabolic lateralization in the putaminal area. Manual ROIs were drawn and the metabolism was calculated and compared to a group of five healthy men of approximately same age as the patient (mean age 51 years). The asymmetry index (side difference as percentage of mean) showed a right putamen hypermetabolic gradient of +10,4% in the patient, while in the control group there were left side gradient of –3,9%, SD 4,0%. The difference was 2,57 SD indicating a true difference in functional asymmetry compared to the controls. Increased metabolism on the right putamen compared to the left one in the patient was considered pathological and related to the patient's clinical condition and, thereby, a marker of the pathophysiological process of the brain in certain situations of severe somatization.

6. DISCUSSION

6.1 GENERAL DISCUSSION

Functional somatic symptoms are common, and also clinically important. The prevalence of emotional distress and disorder in patients who attend hospital with functional syndromes (such as irritable bowel syndrome) is higher than in patients with comparable medical conditions (such as inflammatory bowel disease) (Walker et al. 1990). Furthermore, far from merely representing the "worried well", many such patients are severely disabled. For example, CFS is associated with worse disability than conditions like heart failure (Komaroff et al. 1996).

This study originated from the need to explore patient group with somatization disorder and undifferentiated somatoform disorder characterized by multiple somatic symptoms which had lasted for a long period and caused functional disability.

The cognitive-affective neuroscience of somatization disorder and related conditions suggests that overlapping psychobiological mechanisms mediate depression, anxiety, and somatization symptoms (Stein and Muller 2008). This series of studies aimed at explore the patients' neurobiological processes in the brain during severe somatization. The findings suggest CNS metabolic and structural changes in patients with somatization disorder and undifferentiated somatoform disorder.

6.2 STUDY I

Study I looked at the rCMRGlc in women with somatization disorder or undifferentiated somatoform disorder and without comorbidities compared with healthy volunteers. The major finding in this exploratory study was that several cerebral regions showed reduced brain metabolism in patients and a trend for even more wide spread cerebral hypometabolism was seen.

There are findings of decreased regional cerebral blood flow (rCBF) in the thalamus and in the caudate nucleus in FM, but not limited entirely to these areas. Low rCBF has been observed also in patients with pain due to metastatic breast cancer and to traumatic peripheral neuropathy (Di Piero et al. 1991, Iadarola et al. 1995). Abnormally low rCBF levels in the caudate nucleus have been documented in patients with pain related to spinal cord injury as well as in restless leg syndrome (Ness et al. 1998, San Pedro et al. 1998). The caudate nucleus receives a large nociceptive input from spinal pain pathways, including both nociceptive-specific neurons that signal the presence of pain, and wide-dynamic-range neurons that provide graded responses throughout the range of innocuous and painful stimulation (Chudler et al. 1993, Diorio et al. 1993, Sorkin et al. 1992). The caudate nucleus may also have a role in intrinsic analgesia systems (AACG 1977, Lineberry and Vierck 1975).

Cerebral metabolism and blood flow are not identical measures, but reflect well the activity in cell function, thus blood flow being more rapid in response to environmental stimuli.

Neuropsychological tests show that FM patients perform below average in tests of both working memory and long-term memory (Leavitt and Katz 2006, Park et al. 2001). In particular, patients seem to have difficulties with tasks in which competing stimuli are presented and that require, therefore, some degree of stimulus inhibition (Leavitt and Katz 2006). There is large amount of existing evidence demonstrating mesocortical and striatal dopaminergic pathways importance in memory tasks, perceptual speed, and response inhibition (Bäckman et al. 2006). The patients in study I showed also neuropsychological impairment: the performance was inferior in tests involving semantic memory, verbal episodic memory and visuospatial tasks, and they were slower in attentional tasks compared with healthy controls (Niemi et al. 2002).

Based on the findings in somatization and FM, common neurobiological processes may be involved in both clinical conditions, and dopaminergic neurotransmission may play an important role in the pathophysiology of somatization disorder and undifferentiated somatoform disorder.

6.3 STUDY II

Study II investigated the brain morphology of women with somatization disorder or undifferentiated somatoform disorder compared to healthy controls. Based on observations from study I, it was assumed that some cerebral volumetric differences may be seen between groups. The main finding was bilateral volume increase of the caudate nuclei in patients.

FM has often been described as a stress-related disorder (Staud 2007). The observation of decreased gray matter density in the perihippocampal gyrus is of particular interest. Similar neuroanatomical abnormalities have been reported in other stress-related disorders, including chronic fatigue syndrome and posttraumatic stress disorder (Okada et al. 2004, Villarreal et al. 2002).

Voxel based morphometry performed in FM patients revealed a conspicuous pattern of altered brain morphology in the right superior temporal gyrus (decrease in grey matter), the left posterior thalamus (decrease in grey matter), in the left orbitofrontal cortex (increase in grey matter), left cerebellum (increase in grey matter) and in the striatum bilaterally (putamen area, increase in grey matter) (Schmidt-Wilke et al. 2007). In CFS patients cerebral gray matter volumetric changes (reduction) were not local (de Lange et al. 2005).

In patients with somatization disorder or undifferentiated somatoform disorder we detected an increased volume of caudate nuclei, and furthermore, on supplementary analysis, a decrease of volume in the left hippocampus. More data is required to compare the similarities and differences of these disorders. Current evidence is limited, but suggests that hippocampal atrophy may be one shared phenomenon, also seen in

depression. However, neither MDD MRI studies show no increase in caudate nuclei nor FM or CFS. Increased caudate volume remains a distinguishing factor between SD and undifferentiated somatoform disorder versus MDD, FM and CFS. There is a possibility that the finding is primarly related to the somatization disorder as predisposing factor. On the other hand, the volume change in this patient group may be a compensatory phenomenon of long-lasting stress and reduction of metabolism seen in the same brain structure. The reduction in hippocampal volume in the left may be stress-related as similar finding has been described in several MDD studies as well (Konarsky et al. 2008).

6.4 STUDY III

In Study III low NS and high HA as well as reduced glucose metabolism in caudate and putamen nuclei was associated with severe somatization.

Initially, Cloninger suggested a temperamental pattern of high NS and low HA to be associated with somatization. Those temperament factors would cause impulsiveness and disposition toward excitability, leading ultimately to chronic somatic anxiety (Cloninger 1986). Our observation suggested an opposite pattern of temperament. Due to the stable nature of SD and undifferentiated somatoform disorder, it is unlikely that these results would reflect the state of the patients. High HA has been reported to be associated with somatization, but the reports have been controversial or single observations (Battaglia et al. 1998, Grabe et al. 2004, Karvonen et al. 2006, Russo et al. 1994). However, no support for the original theory of somatization and its association to certain temperamental dimensions has been presented.

In our study the strongest association for somatization was reduced glucose metabolism in caudate nuclei. We considered it to be a trait marker of the pathophysiology of the disorder itself. Temperament factors are possibly more general, non-specific features associated with somatization. These features may lead to emotional processing in a burdening way, and consequently facilitate the development of the disorder.

6.5 STUDY IV

In Study IV a right putamen hypermetabolic gradient exceeding 10% was observed compared to the left one measured with [18F]FDG-PET. This was greater than 2SD aberration seen in the healthy volunteer group and probably reflected the multiple somatic complaints of the patient with left side gradient symptoms.

The neurobiological findings of the case were different compared to our observations in the group of severely somatizing women. The left side symptom gradient is in line with contralateral findings in the brain. This observation suggest that even though multiple somatic symptoms occurred, the left side gradient may suggest another kind of pathology involved. The findings also support the idea of neurobiological variety in somatization.

6.6 METHODOLOGICAL DISCUSSION

PET method allows quantification of regional tracer accumulation, [18F]FDG, with great precision. It also provides relatively good spatial resolution and gives an opportunity to, almost, non-invasively assess regional tissue metabolism. Exposure of the subjects to ionizing radiation is obviously the disadvantage of the PET method. This issue is of special importance when studying healthy control subjects, children and those who have limited competence to understand the risks and benefits presented in IC. The expenses of radiotracer production, maintenance and operation of a PET facility also limit the use of PET. The LC correction factor is used to correct for any differences in the transport and phosphorylation between [18F]FDG and glucose when converting the clearance rates of [18F]FDG to those of glucose.

MRI method allows precise anatomical images without exposing subjects to ionizing radiation. Magnetizing items (i.e. iron item or any other magnetizing metal) in the body are the contraindication for the use of this non-invasive technique. In brain imaging, MRI provides a valuable tool in differentiation of structures and allows volumetric measurements to be made with good resolution.

TCI method allows us to assess the personality of the subject categorized under seven dimensional factors. Four temperament and three character factors form the individual personality dimensions. The four temperament factor profiles are hypothesized to be independently heritable, stable, and manifesting early in the life. The heritability of each temperament factor has been estimated to range from 50% to 65% (Ando et al. 2002, Ando et al. 2004, Cloninger et al. 1993, Cloninger et al. 1994, Gillespie et al. 2003, Heath et al. 1994, Stallings et al. 1996).

6.7 LIMITATIONS AND STRENGTHS

As we started to collect the patients we soon realized the problem of lacking diagnoses, especially SD diagnoses, in the patient records. Severely somatizing patients were not concentrated in any single health care unit to receive treatment, but floating uncontrolled in the health care system. This resulted in a slow recruitment and required very wide scope when acquiring patient records from different health care units and hence, the possibility to miss some information. The most used medical diagnosis was recognized to be FM when economical or other compensations were given to patients due to medical reasons. Practically, diagnosis of somatization disorder or undifferentiated somatoform disorder was not used and diagnosis had to be established during the screening process. The other problem was psychiatric comorbidities, like anxiety and depression, which are common in patients (Henningsen 2003, Lieb et al. 2007). The requirement to find “pure” somatizing patients without clinical comorbidities led to exclusion of some patients and reduction in statistical power. However, this was considered essential in order to ensure that the results are genuinely associated with somatization. The somatoform disorder diagnostic categories are criticized for lack of validity (Creed and Barsky 2004). The validity of medical diagnoses is regarded as “if they have been shown to be discrete entities with natural

boundaries that separate them from other disorders." (Kendell and Jablensky 2003). There have been few studies of clinical features, biological markers, family aggregation, longitudinal course, or treatment response of somatoform disorders (Kendell 2002, Kendler et al. 1995, Ron 2001). However, not many psychiatric diagnoses are valid according to the criteria above, so the somatoform disorders are not an exception. Many diagnoses have higher utility because they convey information about etiology, pathology, outcome, and treatment response (Kendell and Jablensky 2003). This kind of benefit is generally lacking for the somatoform disorders. This results in rejection of diagnoses by patients who see their problems as physical. Also, the rarity of these disorders, as currently defined, does not reflect the level of somatic distress encountered by clinicians (Allen et al. 2004, Mayou et al. 2005).

The screening procedure of the patients included in this study was multiple-phase. It was considered essential to stepwise collect and analyze the information narrowing the possibility of false positive cases entering the study. Lack of structured clinical interview, SCID, is a limitation of the studies. Structured interviews systematize the information collected and ensure all relevant issues are covered, so, help to avoid false negatives in the case of co-operating patients. Structured interviews, however, neither estimate the symptom content nor the symptom context and attribution, they are related to. This is essential, when setting a clinical diagnosis of SD or undifferentiated somatoform disorder and trying to avoid false positive cases entering the trial. The strength of the selection procedure is its ability to evaluate the nature of the symptoms and set a reliable diagnosis of SD or undifferentiated somatoform disorder. Additionally, the three phase selection procedure reduced the probability of missing important information obtained with a structural method. The importance of the review of the somatic patient records combined with psychiatric interview is also emphasized by Karvonen et al. (2004).

Literature findings on regional differences in cerebral blood flow and metabolism in depression are controversial. Differences between studies may be ascribed to differing subject selection, symptom profiles, clinical states, medication status and image acquisition (Holthoff et al. 2004). These problems apply also to our studies even though somatizing conditions are considered stable in nature and investigational conditions were standardized as much as possible.

The small sample size is very common in PET and MRI studies. This, however, generates restrictions in statistical analysis. Multiple comparison methods become easily too conservative and the probability to detect existing real difference is larger than it should be, as in study I. SPM analyzing method was not available for us at the time the work was done. This fact is faced when there are no earlier observations in the literature and the study is exploratory in nature.

The partial volume effect (PVE) is a possible source of error in imaging studies. PVE is the effect wherein insufficient image resolution leads to a mixing of different tissue types within a voxel. This can lead to inadequate penetration of the deforming surface into the depth of a sulcus and compromise any subsequent quantitative analysis of the local morphology or surface-based spatial normalization. The accuracy of PET and MRI measurement in the human brain is also limited by the resolution of the scanner.

7. SUMMARY AND CONCLUSIONS

7.1 MAIN FINDINGS

The main findings in these studies are that from the standpoint of somatization disorder and undifferentiated somatoform disorder there probably is associated CNS pathophysiology, and therefore these findings suggest that somatization disorder and undifferentiated somatoform disorder can be explained medically as well. Another important observation is that somatization disorder/ undifferentiated somatoform disorder may not be one neurobiological entity.

7.2 CLINICAL IMPLICATIONS

Clinical troubles often raise from the help-seeking behavior of the patients who believe themselves suffering from physical disease. Subjective complaints of somatic ill-being without clear, objective clinical findings may lead to a frustration in doctor patient relationship and "doctor-shopping" in order to get more investigations performed. Different MUS syndromes: SD, CFS, FM share a lot of clinical features and also share observed CNS pathology in each syndrome which might help the clinician understand the multiplicity of symptoms for the patient and the nature of the disease(s). It is recommended that awareness of the pathophysiology of the SD as well as other MUS should be increased among doctors. The best case would be that this would lead to an understanding that patients are really suffering from an organic problem and that the symptoms are neither caused deliberately, mimicked, nor imagined.

7.3 FUTURE RESEARCH IMPLICATIONS

A clarification regarding a number of different syndromes, which all currently bear the background of medically more or less unexplained when it comes to pathophysiology and origin, is indicated. This implies research of the core symptoms of the different syndromes. This might also help to detect the common features of the possibly different disorders and avoid the "old wine in the new bottles" - situation. Comparison of neurobiological findings and other physical measures is implicated between different MUS entities and depression as well.

Due to many reasons, confirmatory studies are required to establish the preliminary findings of FDG-PET and MRI. Also patients with MDD would be good to include into the study as one group, in addition to SD and control group. This would help to differentiate CNS mechanisms between these groups in patients without comorbid psychiatric disorders.

Somatization is seen more often in women than men. Whether there is gender difference existing in CNS pathology, between somatizing men and women, is worth investigating.

More data is required to understand and differentiate the neurobiological (sub)groups of somatizing patients and the specific features related. Current findings encourage the need for more studies with MRI and PET to confirm the results obtained so far. Functional neuroimaging like fMRI and different PET techniques will undoubtedly provide crucial information in the investigation of this patient group. Diffusion tensor imaging provides a valuable tool to investigate the possible axonal problems in the neural networking of the patients. All in all, the cognitive problems described, reflecting deteriorated performance in this patient group, indicate combined assessment of these techniques with imaging.

The CNS structures associated with severe somatization are rich in dopaminergic function and evaluation of dopaminergic system is justified. Dopamine (DA) neurotransmission is known to be associated with attention. Additionally, patients were inferior compared with the controls in several cognitive domains addressed, being particularly, impaired in verbal memory and visuo-spatial skills and performed slowly in attentional tasks demanding working memory and sustained vigilance (Niemi et al. 2002).

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10. APPENDIX

Lomakkeen numero: _____ (Tutkija täyttää)

No.: _____ (Tutkija täyttää)

SCL-90-OIREKYSELYLOMAKE

TÄYTTÖOHJEET

Seuraavilla sivuilla on esitetty luettelo ongelmista ja vaivoista joita ihmisillä esiintyy ajoittain.

Luettuanne kunkin kysymyksen huolellisesti merkitkää ympyröimällä vastausvaihtoehto, joka parhaiten kuvaa sitä, kuinka paljon kyseinen asia on viimeisen kuukauden aikana vaivannut tai ahdistanut Teitä.

Esimerkki:

Missä määrin teitä on viimeisen kuukauden aikana vaivannut

		Ei lainkaan	Melko vähän	Jonkin verran	Melko paljon	Erittäin paljon
1.	Päänsärky	(1)	(2)	(3)	(4)	(5)

Vastatkaa jokaiseen kysymykseen.
Merkitkää vain yksi kohta kustakin kysymyksestä.
Merkitkää tähän lomakkeen täyttöpäivämäärä: _____

KYSYMYKSIÄ SAATTAA TUNTUA OLEVAN PALJON. SILTI ON TÄRKEÄTÄ, ETTÄ JAKSATTE VASTATA HUOLELLISESTI LOPPUUN SAAKKA.

KIITOS JO ETUKÄTEEN VAIVANNÄÖSTÄNNE.

	MISSÄ MÄÄRIN TEITÄ ON VIIMEISEN KUUKAUDEN AIKANA VAIVANNUT	Ei lainkaan	Melko vähän	Jonkin verran	Melko paljon	Erittäin paljon
1.	Päänsärky	(1)	(2)	(3)	(4)	(5)
2.	Hermostuneisuus tai sisäinen rauhattomuus	(1)	(2)	(3)	(4)	(5)
3.	Ajatukset, sanat tai mielikuvat joita ette saa mielestänne	(1)	(2)	(3)	(4)	(5)
4.	Heikotuksen tai huimauksen tunne	(1)	(2)	(3)	(4)	(5)
5.	Seksuaalisen mielenkiinnon tai nautinnon tunteen väheneminen	(1)	(2)	(3)	(4)	(5)
6.	Toisia kohtaan tuntemanne arvostelunhalu	(1)	(2)	(3)	(4)	(5)
7.	Ajatus, että joku voi säädellä ajatuksianne	(1)	(2)	(3)	(4)	(5)
8.	Tunne siitä, että muut ovat syypäitä useimpiin vaikeuksiinne	(1)	(2)	(3)	(4)	(5)
9.	Vaikeus muistaa asioita	(1)	(2)	(3)	(4)	(5)
10.	Pelko, että olette huolimaton tai piittaamaton	(1)	(2)	(3)	(4)	(5)
11.	Tunne, että ärsyynnytte tai suututte helposti	(1)	(2)	(3)	(4)	(5)
12.	Sydän- tai rintakivut	(1)	(2)	(3)	(4)	(5)
13.	Pelontunne avoimilla paikoilla tai kadulla	(1)	(2)	(3)	(4)	(5)
14.	Tarmokkuuden puuttuminen tai väheneminen	(1)	(2)	(3)	(4)	(5)
15.	Ajatukset elämänne lopettamisesta	(1)	(2)	(3)	(4)	(5)
16.	Se että kuulette ääniä, joita muut eivät kuule	(1)	(2)	(3)	(4)	(5)
17.	Vapina	(1)	(2)	(3)	(4)	(5)
18.	Tunne, ettei useimpiin ihmisiin voi luottaa	(1)	(2)	(3)	(4)	(5)
19.	Huono ruokahalu	(1)	(2)	(3)	(4)	(5)
20.	Itkuherkkyys	(1)	(2)	(3)	(4)	(5)
21.	Ujous tai vaivautuneisuus vastakkaisen sukupuolen seurassa	(1)	(2)	(3)	(4)	(5)
22.	Tunne, että olette umpikujassa tai loukussa	(1)	(2)	(3)	(4)	(5)
23.	Pelästyminen äkillisesti ilman mitään syytä	(1)	(2)	(3)	(4)	(5)
24.	Tunteenpurkaukset, joita ette pysty hillitsemään	(1)	(2)	(3)	(4)	(5)
25.	Se, että pelkäätte lähteä yksin ulos kotoa	(1)	(2)	(3)	(4)	(5)
26.	Itsesyytökset	(1)	(2)	(3)	(4)	(5)

	MISSÄ MÄÄRIN TEITÄ ON VIIMEISEN KUUKAUDEN AIKANA VAIVANNUT	Ei lainkaan	Melko vähän	Jonkin verran	Melko paljon	Erittäin paljon
27.	Kivut ristiselässä	(1)	(2)	(3)	(4)	(5)
28.	Tunne, että olette lukossa, ettekä saa asioita hoidetuksi	(1)	(2)	(3)	(4)	(5)
29.	Yksinäisyys	(1)	(2)	(3)	(4)	(5)
30.	Alakuloisuus	(1)	(2)	(3)	(4)	(5)
31.	Liika asioiden murehtiminen	(1)	(2)	(3)	(4)	(5)
32.	Kiinnostuksen puute lähes kaikkeen	(1)	(2)	(3)	(4)	(5)
33.	Pelokkuus	(1)	(2)	(3)	(4)	(5)
34.	Se että loukkaannutte helposti	(1)	(2)	(3)	(4)	(5)
35.	Se että toiset ihmiset ovat tietoisia yksityisistä ajatuksistanne	(1)	(2)	(3)	(4)	(5)
36.	Tunne, että muut ihmiset eivät ymmärrä Teitä tai eivät tunne myötätuntoa Teitä kohtaan.	(1)	(2)	(3)	(4)	(5)
37.	Tunne, että ihmiset ovat epäystävällisiä tai eivät pidä teistä	(1)	(2)	(3)	(4)	(5)
38.	Se, että joudutte tekemään asiat hyvin hitaasti välttääksenne virheitä	(1)	(2)	(3)	(4)	(5)
39.	Sydämentykytykset tai -jyskytykset	(1)	(2)	(3)	(4)	(5)
40.	Pahoinvointi ja vatsavaivat	(1)	(2)	(3)	(4)	(5)
41.	Huonommuudentunne	(1)	(2)	(3)	(4)	(5)
42.	Lihassäryt	(1)	(2)	(3)	(4)	(5)
43.	Tunne, että Teitä tarkkaillaan tai Teistä puhutaan	(1)	(2)	(3)	(4)	(5)
44.	Unensaantivaikeudet	(1)	(2)	(3)	(4)	(5)
45.	Tarve tarkistaa kerran tai useammin se mitä tekee	(1)	(2)	(3)	(4)	(5)
46.	Vaikeus tehdä päätöksiä	(1)	(2)	(3)	(4)	(5)
47.	Se että pelkäätte matkustaa bussissa, metrossa tai junassa	(1)	(2)	(3)	(4)	(5)
48.	Hengenahdistus	(1)	(2)	(3)	(4)	(5)
49.	Kuumat tai kylmät aallot	(1)	(2)	(3)	(4)	(5)
50.	Se että joudutte välttelemään tiettyjä asioita, paikkoja tai toimintoja, koska ne pelottavat Teitä	(1)	(2)	(3)	(4)	(5)
51.	Muisti- tai ajatuskatkot	(1)	(2)	(3)	(4)	(5)
52.	Puutuminen tai pistely jossain ruumiinosassa	(1)	(2)	(3)	(4)	(5)

	MISSÄ MÄÄRIN TEITÄ ON VIIMEISEN KUUKAUDEN AIKANA VAIVANNUT	Ei lainkaan	Melko vähän	Jonkin verran	Melko paljon	Erittäin paljon
53.	Palantunne kurkussa	(1)	(2)	(3)	(4)	(5)
54.	Toivottomuus tulevaisuuden suhteen	(1)	(2)	(3)	(4)	(5)
55.	Keskittymisvaikeudet	(1)	(2)	(3)	(4)	(5)
56.	Heikkouden tunne jossain ruumiin osassa	(1)	(2)	(3)	(4)	(5)
57.	Jännittyneisyys tai kiihtyneisyys	(1)	(2)	(3)	(4)	(5)
58.	Painon tunne käsissä tai jaloissa	(1)	(2)	(3)	(4)	(5)
59.	Ajatukset kuolemasta tai kuolemisesta	(1)	(2)	(3)	(4)	(5)
60.	Ylensyöminen	(1)	(2)	(3)	(4)	(5)
61.	Vaivautuneisuus toisten puhuessa Teistä tai katsellessa Teitä	(1)	(2)	(3)	(4)	(5)
62.	Tunne ajatuksista, jotka eivät ole omianne	(1)	(2)	(3)	(4)	(5)
63.	Halu lyödä tai muuten vahingoittaa jotakuta	(1)	(2)	(3)	(4)	(5)
64.	Se, että heräätte aikaisin aamulla ettekä enää saa unta	(1)	(2)	(3)	(4)	(5)
65.	Sisäinen pakko toistaa jotain toimintaa (esim. koskettaminen, laskeminen tai peseminen)	(1)	(2)	(3)	(4)	(5)
66.	Levoton ja katkonainen uni	(1)	(2)	(3)	(4)	(5)
67.	Pakonomainen halu rikkoa tai paiskoa esineitä	(1)	(2)	(3)	(4)	(5)
68.	Ajatukset tai uskomukset, joita muut eivät ymmärrä	(1)	(2)	(3)	(4)	(5)
69.	Häiritsevä tietoisuus omasta olemisesta toisten ihmisten seurassa	(1)	(2)	(3)	(4)	(5)
70.	Epämukavuuden tunne ollessanne ihmisten keskellä, esim. kaupoissa tai elokuvissa tms.	(1)	(2)	(3)	(4)	(5)
71.	Tunne, että koko elämä on jatkuvaa ponnistelua	(1)	(2)	(3)	(4)	(5)
72.	Pelon tai pakokauhun puuskat	(1)	(2)	(3)	(4)	(5)
73.	Epämukavuuden tunne ollessanne aterioimassa tai kahvilla julkisella paikalla	(1)	(2)	(3)	(4)	(5)
74.	Joutuminen usein väittelyihin	(1)	(2)	(3)	(4)	(5)
75.	Hermostuneisuus jäädessänne yksin	(1)	(2)	(3)	(4)	(5)
76.	Tunne, etteivät toiset anna tarpeeksi arvoa saavutuksillenne	(1)	(2)	(3)	(4)	(5)
77.	Yksinäisyyden tunne silloinkin, kun olette toisten seurassa	(1)	(2)	(3)	(4)	(5)
78.	Levottomuuden tunne, joka estää rauhassa istumisenkin	(1)	(2)	(3)	(4)	(5)

	MISSÄ MÄÄRIN TEITÄ ON VIIMEISEN KUUKAUDEN AIKANA VAIVANNUT	Ei lainkaan	Melko vähän	Jonkin verran	Melko paljon	Erittäin paljon
79.	Arvottomuuden tunteet	(1)	(2)	(3)	(4)	(5)
80.	Tunne, että tutut asiat ovat outoja tai epätodellisia	(1)	(2)	(3)	(4)	(5)
81.	Halu huutaa tai heitellä esineitä	(1)	(2)	(3)	(4)	(5)
82.	Pelko, että pyörtyisitte yleisellä paikalla	(1)	(2)	(3)	(4)	(5)
83.	Tunne, että ihmiset yrittävät hyötyä kustannuksellanne, jos annatte siihen tilaisuuden	(1)	(2)	(3)	(4)	(5)
84.	Seksuaalisuutta koskevat, häiritsevät asiat	(1)	(2)	(3)	(4)	(5)
85.	Ajatus, että Teitä pitäisi rangaista synneistä	(1)	(2)	(3)	(4)	(5)
86.	Tunne, että Teitä painostetaan tekemään tehtävänne	(1)	(2)	(3)	(4)	(5)
87.	Tunne, että jotakin on vakavasti vialla ruumiissanne	(1)	(2)	(3)	(4)	(5)
88.	Tunne, ettette koskaan ole ollut läheinen kenenkään kanssa	(1)	(2)	(3)	(4)	(5)
89.	Syyllisyydentunteet	(1)	(2)	(3)	(4)	(5)
90.	Tunne, että "päässänne on jotain vikaa"	(1)	(2)	(3)	(4)	(5)

Tarkistaisitteko vielä ystävällisesti, että olette muistaneet vastata jokaiseen kysymykseen.

KIITOS VAIVANNÄÖSTÄ!