IDIOPATHIC ENVIRONMENTAL INTOLERANCE ATTRIBUTED TO ELECTROMAGNETIC FIELDS

- PHYSIOLOGICAL AND PSYCHOLOGICAL ASPECTS

Amanda Johansson

Umeå 2008
Kong Christian stod ved højen mast
men han var inte gjort af plast.
Emedan han av plast ej var
står han inte längre kvar.

Tage Danielsson
Abstract
Idiopathic Environmental Intolerance Attributed to Electromagnetic Fields - Physiological and Psychological Aspects
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Symptoms attributed to electromagnetic field (EMF) exposure have been reported since the 1970s. The symptoms reported vary widely as do the sources to which the symptoms are attributed. No associations between symptoms and EMF exposure have been objectively demonstrated, and the condition is regarded as a subtype of idiopathic environmental intolerance; symptoms attributed to environmental factors at levels tolerated by the majority of people.

This thesis aims to increase the knowledge of different groups of people with symptoms attributed to EMF by investigating the effects of EMF exposure and by additional description of the heterogeneous group of persons reporting symptoms attributed to EMF.

The effect of mobile phone (MP)-like radio frequency (RF) fields on symptoms, autonomic nervous system (ANS) parameters (e.g. heart rate variability, HRV), short-term memory, and reaction time in persons with symptoms attributed to the use of MP (MP subjects) was investigated in a provocation study. A second provocation study investigated the effect of similar exposure on serum concentration of biomarkers in persons with skin symptoms not attributed to EMF exposure (atopic dermatitis).

No effect of exposure was detected in either of the two studies. Compared to controls, MP subjects displayed changes in HRV during cognitive tests, but not during rest. This contrasts with earlier findings, where an elevated sympathetic nervous system activity was found in subjects with symptoms attributed to EMF sources in general (EHS subjects) both during cognitive tests and during rest.

Proposed differences between subgroups of persons with EMF-related symptoms with respect to symptoms, stress, exhaustion, and self-reported personality traits were investigated in a cross-sectional questionnaire study. MP participants reported primarily symptoms from the head, whereas EHS subjects reported symptoms from many organ systems. The latter also reported inability to work and diminished quality of life due to symptoms attributed to EMF to a higher extent. Furthermore, EHS participants reported higher levels of anxiety, depression, perceived stress, and exhaustion when compared with a population based reference group. MP participants reported higher levels of anxiety and exhaustion only.

In a pilot study, 24-hour and short-term HRV were investigated in EHS subjects, to examine whether the imbalance between sympathetic and parasympathetic activity observed in the same subjects in 24-h HRV recordings seven years earlier would still be present. There was a general indication of increased parasympathetic activity compared with earlier recordings, and a reduction of symptoms. The overall pattern was similar between 24-h and short-term recordings for each subject, however, there were large between-subject differences.

The results presented in this thesis do not support the hypothesis of an effect of MP-like RF exposure on symptoms, ANS activity, CFFT, cognitive function, or serum concentrations of biomarkers. However, they do provide support for the hypothesis that persons with symptoms attributed to EMF who differ in the attribution of their symptoms (MP and electrical equipment in general) may also differ with respect to ANS activity and certain psychological aspects.

Keywords: Electrical Hypersensitivity, EHS, Mobile Phone, MP, Heart Rate Variability, HRV, Provocation Study, Radiofrequency Field.
Symptom relaterade till exponering för elektromagnetiska fält (EMF) har rapporterats sedan 70-talet. Symptombilden varierar, liksom källorna de relateras till. Något klart samband mellan symptom och exponering för EMF har inte kunnat påvisas i kontrollerade studier.

Syftet med denna avhandling är att öka kunskapen om olika grupper som attribuerar symptom till EMF, dels genom att undersöka effekterna av exponering för EMF och dels genom att beskriva de olika grupperna där symptomattribueringen varierar, i detta fall personer med mobiltelefon(MP)-relaterade symptom och personer med symptom relaterade till exponering för EMF generellt (EHS).

I en provokationsstudie undersöks effekten av radiofrekventa (RF) signaler motsvarande de som emitteras från en GSM MP på symptom, autonoma nervsystemet (ANS; t.ex. hjärtfrekvensvariabilitet, HRV), kritisk flimmerfrekvens (CFFT) samt arbetsminne och reaktionstid hos personer med MP-relaterade symptom. I ytterligare en provokationsstudie undersöks effekten av samma exponering på koncentrationen av tre biomarkörer i serum hos personer med hudsymptom utan relation till exponering för EMF (personer med atopiskt eksem).

Ingen effekt av exponeringen kunde påvisas i någon av studierna. Däremot uppskattades gruppen med MP-relaterade symptom ökad sympatikusaktivitet jämfört med en kontrollgrupp under kognitiva tester; däremot inte i vila. Resultatet avviker från tidigare studier av personer med EHS där en ökad sympatikusaktivitet påvisades såväl i vila som under kognitiva tester.

I en enkätstudie studerades skillnader i rapporterad symptomförekomst och ett antal psykologiska aspekter hos olika grupper med symptom relaterade till EMF (personer med MP-relaterade symptom och personer med EHS). Personer med MP-relaterade symptom rapporterade framför allt symptom från huvudregionen, medan personer med EHS rapporterade en mer komplext symptombild. Den senare gruppen
rapporterade ofta oförmåga till arbete och sämre livskvalitet på grund av sina EMF-relaterade symptom. Vidare uppgav gruppen med EHS högre grad av ångest, depression, upplevd stress och utmattning än en populationsbaserad referensgrupp, medan gruppen med MP-relaterade symptom uppgav högre grad av ångest och utmattning än referensgruppen, men över lag skattade lägre än gruppen med EHS.

I syfte att undersöka huruvida en tidigare påvisad obalans mellan sympatikuss- och parasympatikusaktivitet förändras över tid utfördes en 7-års uppföljning av 24-timmars HRV registrering på fem personer med EHS. Vidare jämfördes 24-timmarsregistreringen med en korttidsregistrering av HRV. Resultaten indikerade en ökning av parasympatikusaktivitet och en minskning av EMF-relaterade symptom jämfört med den tidigare registreringen. Korttidsregistreringarna och 24-timmars registreringarna antydde ett likartat mönster, men med stora individuella skillnader, och det lilla antalet undersökta individer medgav inga generella slutsatser.

Sammantaget ger resultatet av studierna inget stöd för hypotesen att exponering för radiofrekventa GSM signaler skulle orsaka symptom eller påverka ANS aktivitet, CFFT, kognitiv funktion, eller biomarkörer. Däremot finns stöd för hypotesen att det skulle föreligga skillnader mellan grupper med olika symptomattribuering (endast MP respektive elektrisk utrustning i allmänhet) med avseende på ANS aktivitet och vissa psykologiska aspekter.
# Abbreviations and definitions

## Technical terms/units

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>EMF</td>
<td>Electromagnetic field/ -s</td>
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<tr>
<td>GSM</td>
<td>Global system of mobile communication</td>
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<tr>
<td>Hz</td>
<td>Frequency in Hertz</td>
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<td>MP</td>
<td>Mobile phone/ -s</td>
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<tr>
<td>RF</td>
<td>Radio frequency</td>
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<tr>
<td>SAR</td>
<td>Specific Absorption Rate in W/ kg</td>
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<td>VDT</td>
<td>Visual display terminal/ -s</td>
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## Medical related terms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AD</td>
<td>Atopic dermatitis</td>
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<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
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<td>BDNF</td>
<td>Brain derived neurotrophic factor</td>
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<tr>
<td>CBT</td>
<td>Cognitive behavioural therapy</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CFFT</td>
<td>Critical flicker fusion threshold</td>
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<tr>
<td>EHS</td>
<td>Perceived electromagnetic hypersensitivity</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<tr>
<td>HR</td>
<td>Heart rate (beats/ min)</td>
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<td>HRV</td>
<td>Heart rate variability</td>
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<tr>
<td>VLF</td>
<td>Very low frequency band (≤ 0.04 Hz)</td>
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<tr>
<td>LF</td>
<td>Low frequency band (&gt;0.04-0.15 Hz)</td>
</tr>
<tr>
<td>HF</td>
<td>High frequency band (&gt;0.15 Hz)</td>
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<tr>
<td>PTOT</td>
<td>Total power in the frequency band</td>
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<tr>
<td>PHFn</td>
<td>=PHF/ [PTOT-PVLF]</td>
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<tr>
<td>PLFn</td>
<td>=PLF/ [PTOT-PVLF]</td>
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<tr>
<td>IEI</td>
<td>Idiopathic environmental intolerance</td>
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<tr>
<td>SP</td>
<td>Substance P</td>
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<tr>
<td>TNF-α</td>
<td>Tumor necrosis factor α</td>
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<tr>
<td>TNF R1</td>
<td>Tumor necrosis factor receptor 1</td>
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Original studies

This thesis is based on the following studies, referred to by Roman numerals:


III Johansson A., Nordin S., Heiden M., Sandström M. Symptoms, Personality Traits, and Stress in People with Mobile Phone-Related Symptoms and Electromagnetic Hypersensitivity. (Submitted to Journal of Psychosomatic Research)


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Introduction

Idiopathic environmental intolerance (IEI) includes a number of disorders attributed to the exposure of environmental factors at levels that are well below known limits for toxicity, and that are tolerated by most people [1]. Although IEI involves multiple symptoms from several organ systems, there is no characteristic symptom picture. Several environmental exposures are associated with the development of symptoms; chemicals with or without odours, foods, drugs and electromagnetic fields [2]. Most provocation studies have failed to demonstrate a causal relationship between exposure and symptoms, and so far there are no accepted theories of underlying mechanisms. This thesis will focus on IEI attributed to exposure to electromagnetic fields (EMF).

From the time the first reports related perceived symptoms to electrical equipment, the association between symptoms and EMF exposure has been disputed. Regardless of the association between IEI and EMF, the afflicted individuals suffer real health problems, and the consequences may be substantial in terms of physical and psychological discomfort, decreased working capacity, and in severe cases social isolation. Presently, few treatments are available, and there is uncertainty concerning how to efficiently handle cases of IEI in health care as well as in the workplace and general public settings. In addition to the impact of the condition for afflicted individuals, the costs to society in terms of health care consumption and sick leave are likely to be considerable.

Health effects of EMF

EMF are present everywhere in our environment, generated by both natural and man-made sources. The rapid technical development and constantly increasing use of electrical devices during the last decades have further increased our daily exposure to EMF of various frequencies. The frequency, or corresponding wavelength, of the EMF is one of the most important parameters when considering biological effects of EMF exposure. In the low frequency range (<100 kHz) we find emission from electrical equipment such as handheld tools, house hold equipment, and power lines. At higher frequencies, from 100 kHz to 300 GHz, also known as the radio frequency range (RF), exposure originates mainly from mobile phones (MP) and other wireless communication systems,
and from various industrial equipment such as plastic welding machines and glue dryers. Acute effects of exposure to strong EMF fields are well known, and exposure is controlled by national as well as international regulations and guidelines [3-5]. The acute effect of EMF exposure in the low frequency range is nerve excitation due to current induced in the body; the effects of EMF exposure in the RF range arise from the heating of human tissue either locally or as a rise in core temperature.

The effects of long-term EMF exposure at levels that do not cause immediate injury are less well understood. Some epidemiological studies indicate an association between EMF exposure in the power frequency range (50-60 Hz) and increased risk of cancer, e.g., leukaemia, for residential as well as for occupational exposure, whereas others do not. Long-term exposure to power frequency fields is classified as possibly carcinogenic (class 2B) by IARC [6, 7]. Some studies indicate an increased risk of neurodegenerative diseases in highly EMF exposed occupations [8]. The possibility of an association between EMF exposure and cardiovascular disease has been mentioned, but the number of investigations on this topic is limited. There are indications of an increased risk of acute myocardial infarction in highly exposed occupations [9, 10]. Data on the risk of death from arrhythmic heart disease are inconclusive.

Animal studies show divergent results. The findings are not always easily interpreted, due to large methodological differences between studies, insufficient characterization of the exposure etc. [11]. In the low frequency range, effects of weak EMF on cells - such as induction of various stress proteins and changes in chromosomal structure and gene expression - have been demonstrated. It is still under discussion, if the observed effects truly indicate a risk of adverse health effects in humans [11, 12].

For low level chronic exposure to low frequency fields (e.g., residential exposure), there are no exposure limits. However, the Swedish authorities have adopted a precautionary principle, stating that “if measures generally reducing exposure can be taken at reasonable expense and with reasonable consequences in all other respects, an effort should be made to reduce fields radically deviating from what could be deemed normal in the environment concerned” [13]. This statement is primarily based on non-discountable cancer risks.

The effects of long-term exposure to RF fields have attracted attention during the last decade due to the intensive use of MP, but the results are
inconclusive. The main topics of interest have been an increased risk of certain brain tumours, effects on the integrity of the blood-brain barrier and effects on various cognitive processes [14]. Due to the uncertainties regarding the possible health risks from low level RF exposure, mainly those of brain tumours, the Swedish authorities recommend a precautionary approach to the use of MP [15].

A general problem in studies of biological effects of long-term, low level EMF exposure is the uncertainty concerning exposure assessment. Since no mechanisms for such effects are known, it is not possible to identify the importance of various exposure characteristics for possible adverse effects, making it difficult to estimate the “dose”.

**EMF-related symptoms**

In the 1970s, when visual display terminal (VDT) work was introduced, office workers started to report skin symptoms and general symptoms related to the use of VDT [16-20]. EMF emitted from the VDT screen was one of the suggested causes of the symptoms.

In the late 1980s, Knave et al. described a group of patients characterized by multisymptomatic health complaints [21]. Skin symptoms as well as neurasthenic symptoms (e.g., fatigue, dizziness, headaches) were commonly reported. Later on, the condition was labelled “hypersensitivity to electricity” by the afflicted persons themselves, based on their experience that the symptoms were caused by EMF exposure [22]. With the establishment of mobile communication as a part of everyday life in the 1990s, symptoms associated with MP use and to MP base stations were reported as well.

A number of labels other than “hypersensitivity to electricity” have been used to denote symptoms attributed to EMF exposure, e.g., “electrical sensitivity” [23], “sensitivity to electromagnetic fields” [24] and, perhaps most frequently, “electromagnetic hypersensitivity” [25]. The terms “electrical sensitivity” and “electrical sensibility” have further been used to differ between symptoms attributed to EMF exposure and the ability to perceive EMF or an electric current respectively [26, 27]. “Sensitivity” has, somewhat confusingly, been used to denote both symptoms and detection limit [26, 28]. Several of the terms mentioned imply a causal relationship between symptoms and EMF exposure and/or an immunologic origin of the symptoms, none of which have been demonstrated. The World Health Organization (WHO) has proposed a
grouping of various kinds of symptoms attributed to environmental exposures at levels tolerated by the majority of people under the descriptive label “idiopathic environmental intolerance” to avoid all implications about etiology or biological mechanisms. IEI with EMF-attributed symptoms would be labelled IEI-EMF [29].

In this text, the term “EMF-related symptoms” is used to denote all symptoms that individuals attribute to EMF exposure. Subgroups of EMF-related symptoms are labelled after the EMF source to which the afflicted individual attributes the symptoms; symptoms attributed to the use of visual display terminals (VTD-related symptoms), symptoms attributed to the use of mobile phones (MP-related symptoms) and symptoms attributed to the use of electrical equipment in general, perceived electromagnetic hypersensitivity (EHS).

**Prevalence and characteristics of EMF-related symptoms**

Epidemiological studies of EHS have reported a prevalence of 1.5-5% [30-34]. The numbers and the nature of the symptoms differ somewhat between countries. In Sweden, skin symptoms predominate, whereas in Austria and Germany neurasthenic symptoms have been most commonly reported [25, 35]. There are also differences with respect to in which settings the symptoms are primarily experienced and which sources are most frequently reported as the perceived cause of the symptoms. These differences between countries are not easily explained. Differences in the awareness of EMF as a possible health risk, risk perception media coverage, understanding of the concept of EMF-related symptoms, and the general classification of unspecific symptoms have been suggested as factors contributing to the geographical variations [25]. The assessment of prevalence is further limited by the lack of a case definition and of objective measures. The numbers retrieved will be different, because of the way the symptoms are defined.

In a study among office workers in northern Sweden performed in 1989, facial skin symptoms, not necessarily attributed to EMF exposure by the afflicted individuals, were reported twice as often among VDT-operators as in non-operators [36]. An epidemiological study among 17000 MP users in Norway and Sweden found that headache, general discomfort, concentration difficulties, and sensations of warmth on or around the ear increased both with the number of MP calls per day and with the MP calling time per day [37]. Most of the respondents did, however, not report symptoms associated with other electrical appliances. The study
further indicated differences in symptom prevalence between countries. In Norway 31% of the responders experienced at least one symptom associated with MP use, whereas the corresponding number in Sweden was 13% [38].

The nature and the severity of the symptoms vary considerably between individuals, and even if certain symptoms are more common than others, it has been impossible to identify a characteristic symptom complex. The identification of the symptoms as “EMF-related” is based solely on the individual’s attribution. Several attempts have been undertaken, but no causal relationship between symptoms and EMF exposure has been established. Moreover, individuals with EMF-related symptoms have not demonstrated an ability to detect the presence or absence of EMF [27, 39].

Among the most common EMF-related symptoms are facial skin symptoms (e.g., erythema; sensations of heat, tingling and/or tightness; rashes), neurasthenic symptoms (e.g., dizziness, fatigue, feelings of general discomfort, headache, and sleeping disorders) and cognitive symptoms (concentration difficulties and memory loss) [30, 35]. Afflicted individuals, however, report a variety of other symptoms. Groups that attribute their symptoms to different EMF sources to some extent also differ with respect to the symptom picture, but the variation within these groups is still high. People with symptoms attributed only to the use of VDT predominantly report skin symptoms and to some extent also neurasthenic symptoms such as fatigue and general discomfort [40]. People with symptoms attributed only to the use of MP predominantly report facial skin symptoms (mainly sensations of heat on or around the ear), headaches and cognitive symptoms [37]. People with symptoms attributed to electrical equipment in general tend to report more symptoms than people with symptoms attributed to a single EMF source; they also report more neurasthenic symptoms [40].

For several individuals with symptoms attributed to electrical equipment in general, the symptoms were first perceived in association with the use of a single EMF source (usually VDT) and generalized with time, and the view on EMF-related symptoms as progressive, gradually extending from few sources and symptoms is not uncommon [41]. However, there are so far no indications that EMF-related symptoms are generally progressive; on the contrary, many of those with VDT-related symptoms have been found to improve with time [42].
It has been proposed that the heterogeneous group of persons with EMF-related symptoms should be divided into subgroups according to the EMF source to which the symptoms are attributed since clinical experience suggests differences associated with symptom attribution [29, 43]. So far, the WHO distinguishes between symptoms attributed to VDT, MP and/or MP base stations, power lines, or other EMF sources. The idea of subgroups of EMF-related symptoms is, however, not new. Persons with VDT-related symptoms have been found to differ from persons with EHS with respect to illness severity, personality, development of symptoms with time, and social impact of the symptoms [42, 44, 45].

Association between EMF-related symptoms and EMF exposure

Despite several attempts, it has not been possible to confirm an association between EMF exposure and symptoms in provocation studies [27, 39]. Subjects with EMF-related symptoms tend to experience more symptoms than control subjects regardless of exposure condition (exposure/sham exposure), but EMF exposure has not been demonstrated to elicit symptoms in double blind provocation.

A large number of studies examine the effect of EMF exposure on cognitive functions such as reaction time and short-term memory [46]. Most of the recent studies have investigated possible effects of MP or MP base station exposure. The results are inconsistent. Koivisto et al. [47] found slightly improved cognitive function after MP exposure, but other studies have not confirmed this finding [48, 49]. However, in a recent study, a decreased reaction time and increased accuracy were observed in working memory tests following 30 minutes MP exposure [50].

Measurements of the EMF exposure of individuals with EMF-related symptoms have not confirmed the assumption that these individuals would be exposed to higher levels of EMF than those who do not develop symptoms [51]. There are no data describing a possible overrepresentation of EMF-related symptoms in occupations where the EMF exposure is high, e.g., among welders and engine drivers. In contrast, so far, cases are most frequently encountered in environments where the exposure is low, e.g., in offices.
Association between EMF-related symptoms and other factors

Several factors have been reported to be associated with EMF-related symptoms, such as female gender, age, and psychosocial work load, as well as various psychological aspects [40]. Individuals with EMF-related symptoms have been described as distressed, reporting higher levels of stress, depression, and anxiety compared with controls [44, 52]. Other aspects discussed are stress susceptibility and persistence, characteristics that may represent personalities that could be vulnerable in a demanding environment [53, 54]. The findings further indicate that many individuals with EMF-related symptoms become socially isolated, both in their private and in their occupational lives [44]. It is, however, uncertain to which extent the observations represent risk factors for development of EMF-related symptoms or to what extent they represent a consequence of the condition.

Studies of subjects with EHS indicate that this group has an imbalance in the autonomic nervous system (ANS) toward sympathetic predominance. Signs of elevated sympathetic activity, as measured by heart rate variability (HRV) and electrodermal activity, has been observed both in the resting condition and in response to physical (sound, flickering light) and cognitive stressors [55, 56]. In addition to a hyper-responsiveness to flickering light, subjects with EHS have also displayed a higher critical flicker fusion threshold (CFFT) compared to controls, i.e. a higher sensitivity to flickering light. This may contribute to the frequent complaints related to fluorescent lighting and cathode ray tube VDT [57, 58]. Furthermore, an investigation of 24-h HRV in EHS subjects revealed HRV changes interpreted as a sign of night-time parasympathetic withdrawal [59].

Investigations of cortical excitability have encountered differences between subjects with EHS and controls [60, 61]. The results were ambiguous (decreases in younger subjects, and increases in older subjects), but were interpreted as another sign of an irritability of the nervous system in persons with EHS.

Although no medical disease is known to be part of the clinical picture of EMF-related symptoms, afflicted individuals generally report poorer health status than referents [22]. These individuals report more allergies and hypersensitivities of various kinds, asthma, hay fever and common colds than referents.
Treatment of EMF-related symptoms

Little research has been conducted concerning the effectiveness of treatments for EMF-related symptoms. Of the treatments investigated, cognitive behavioural therapy (CBT) has shown some beneficial effects, whereas acupuncture and antioxidant supplementation has not [62]. CBT is directed as much toward cognitive re-evaluation and coping with an insufferable situation as toward changing the actual causes of this situation and has been used successively also for diseases of an unquestionable somatic origin [63]. Consequently, the patient’s beliefs concerning the association between EMF exposure and symptoms need not necessarily be addressed to achieve an improvement of well-being and daily functioning [22, 64]. Recent data actually indicate that information about a person’s ability to detect EMF does not affect beliefs about being adversely affected by EMF to the extent that might be expected or reduce symptoms [65]. The duration of the effects of CBT is not known.

There is no solid basis for a general alteration of the electromagnetic environment (“electromagnetic sanitation”) as a measure to reduce EMF-related symptoms [25, 62, 66]. As most provocation studies so far have failed to demonstrate a clear relationship between exposure and symptoms, it is impossible to tell what alterations would be beneficial. However, a general improvement with respect to environmental factors known to cause similar unspecific symptoms, e.g., indoor air quality, noise, lighting and ergonomic and psychosocial factors, may often result in a decrease of symptoms and has been recommended [25]. As most cases of EMF-related symptoms are encountered in settings where the exposure is low, the question of good environmental conditions in this respect is usually not one of hygienic exposure limits.
Aims

This thesis aims to increase the knowledge of different groups of people with symptoms attributed to EMF by further investigating the effects of EMF exposure and by providing additional description of the heterogeneous group of persons reporting symptoms attributed to EMF with respect to physiological and psychological aspects.

Specific aims:

The specific aims of this thesis are:

- to investigate the effects of exposure to MP-like RF electromagnetic fields on symptoms, physiological parameters, CFFT, cognitive function, and biomarkers;
- to study if persons with EMF-related symptoms could be divided into different subgroups with respect to symptoms, physiological parameters, CFFT, and cognitive function;
- to compare persons with EHS and persons with MP-related symptoms with respect to symptoms, self-reported personality traits, anxiety, depression, exhaustion, and stress.
Material and methods

General methodological aspects

This thesis is based on the results from four studies, three (Studies I, II and IV) laboratory studies and one (Study III) a survey. The studies were conducted using quasi-experimental (Studies I, II and III) and experimental (Study IV) designs. Physiological (Studies I, II, IV) as well as psychological (Studies I, II, III, and IV) variables were investigated.

The first two studies investigated the effects of MP-like exposure on subjects with MP-related symptoms (Study I) and subjects with atopic dermatitis (Study II). In the third study (Study III), groups with EMF-related symptoms attributed to different EMF sources were compared with respect to psychological aspects. The fourth study (Study IV) investigated short-term and 24-h HRV in subjects with EHS. An overview of the research questions and corresponding studies are shown in Figure 1.

Methodological overview of Studies I-IV

Study I

Twenty subjects with MP-related symptoms and 20 control subjects (matched with respect to age and sex) were exposed to a 900 MHz GSM signal. Heart rate, HRV, electrodermal activity, local blood flow and breathing rate were recorded throughout the experiment. CFFT, short-term memory and reaction time were measured before and after exposure/sham exposure. Symptoms during and after exposure/sham exposure were assessed with questionnaires. Physiological parameters, CFFT and results from cognitive tests were analyzed by means of repeated measures analysis of variance (ANOVA); the association between symptoms and exposure using chi-square tests.
Figure 1. Overview of the research questions and papers used in this thesis

**Effect of exposure to MP-like GSM signals on perceived symptoms?**

**Effect of exposure to MP-like GSM signals on physiological parameters, biomarkers and cognitive function?**

**ANS activity in persons with EMF-related symptoms?**

**Personality of persons with EMF-related symptoms?**

**Levels of perceived stress in persons with EMF-related symptoms?**

**Differences between groups / individuals with symptoms attributed to different EMF sources?**

**Study I.**
Effect of MP-like GSM signals on subjects with MP-related symptoms. Physiological recordings, test of CFFT, short-term memory and reaction time, registration of symptoms.

**Study II.**
Effect of MP-like GSM signals on subjects with atopic dermatitis. Physiological recordings, serum concentrations of SP, TNF-α, BDNF, registration of symptoms.

**Study III.**
Differences between persons with EMF-related symptoms with different attribution with respect to symptoms, personality traits, anxiety, depression, exhaustion, perceived stress. Questionnaires.

**Study IV.**
Comparison of short-term and 24-hour HRV in persons with perceived EHS. Follow-up of previous investigation of 24-h HRV. HRV recording, questionnaires.
Study II

Fifteen subjects with atopic dermatitis (AD) and 15 control subjects, matched with respect to age and sex, were exposed to a 900 MHz GSM signal, as in Study I. Baseline heart rate, HRV, electrodermal activity, and local blood flow were recorded. Blood samples were drawn before and after exposure/sham exposure and serum concentrations of Substance P (SP), Tumour necrosis factor receptor 1 (TNF R1) and Brain derived neurotrophic factor (BDNF) were determined with enzyme-linked immunosorbent assay (ELISA). Symptoms during or after exposure/sham exposure were assessed with questionnaires. The effect of exposure on biomarkers was analyzed with repeated measures ANOVA; the associations between symptoms and exposure were not analyzed statistically due to limited symptom reporting.

Study III

Volunteers reporting EMF-related symptoms were presented with seven questionnaires on EMF-related symptoms and various psychological aspects (73% response rate). The participants were assigned to groups according to the EMF source to which they attributed their symptoms: A group with MP-related symptoms (MP group) and a group with symptoms attributed to electrical equipment in general (EHS group). A randomized reference group, selected via the Swedish population register, received similar questionnaires (45% response rate). Since EMF-related symptoms were prevalent also in the reference group, participants without such symptoms were selected from the reference group to form a symptom-free control group for additional comparison. The subgroups of EMF-related symptoms were compared with each other and with the reference group and the control group, respectively. The questionnaire set included a questionnaire on demographics, general health, EMF-related symptoms, and working conditions together with questionnaires assessing personality traits, anxiety, depression, exhaustion, and stress (description of the questionnaire instruments on page 23). Data on psychological aspects were compared between groups by means of multivariate ANOVA.
Study IV

Five subjects with EHS were recruited among the participants of a previous study of 24-h HRV [59]. Short-term and 24-h heart rate variability were recorded. The STAI, the PSQI, and the SMBQ were used to assess anxiety, stress, and exhaustion (description of the questionnaire instruments on page 23). The 24-h HRV recordings from the initial study were compared with the follow-up recordings by means of Friedman’s test. Short-term HRV and results from questionnaires were only examined on individual basis.

EMF exposure

The RF signal used in Study I and II was generated by a test GSM 900 MP and emitted via indoor base station antennas located on each side of the subject’s head (Figure 2). The exposure setup was adjusted to give a rather homogenous SAR distribution in the parietal area of the head with a SAR$_{1g} = 1.0$ W/kg. The exposure was kept below the limits for exposure of the general public, as stated by internationally accepted guidelines of 2 W/kg [3].

With this exposure setup, only the effects of RF exposure were assessed, but not those of the combination of RF and low frequency exposure and temperature increase which is actually present during an MP call. This is different from real-life conditions; however, it makes it possible to draw conclusions about the effect of isolated RF exposure.

Figure 2. Exposure setup used in Studies I and II. The antennas are positioned for provocation (exposure from the right) and the subject’s head is fixed between bars. Electrodes attached for recording of heart rate variability and breathing rate.
Physiological measurements

In Study I, differences in general ANS activity and stress level between the subject groups, and the effect of RF exposure on ANS activity were assessed using heart rate, HRV, respiration, electrodermal activity (EDA) and local blood flow [67, 68]. To enhance reliability, through the probing of several functions, a battery of tests was used.

Heart rate (HR) and HRV were assessed by standard ECG. For heart rate there are clinically accepted limits of normal function, whereas the normal ranges of HRV measures, which reflect the dynamics of the individual response, are less well characterized. EDA is indicative of general sympathetic activity, and is frequently used as a measure of the response to experimental manipulation [68]. EDA was assessed through the measurement of skin conduction measured as the number of electrodermal responses and their intensity. Local blood flow, indicative of sympathetic influence on peripheral circulation, was measured by means of fingertip plethysmogram. Respiration rate, measured by pneumogram, was used mainly as a complement to the HRV analyses.

In Study II, only HR and HRV were assessed. For all recordings and processing an MP100 data acquisition unit (Biopac Systems, Inc., Goleta, CA) and Matlab 6.0 software (Mathworks, Inc., Natick, MA) were used.

Assessment of HRV

Spectral analysis of HRV, a commonly used method, evaluates the overall function of the ANS as well as of the function of the sympathetic and parasympathetic ANS components. The spectral power of the low frequency (LF) component of the HRV is related to baroreceptor-mediated blood pressure control and is considered as an indicator of both sympathetic and parasympathetic activity [69]. At normal breathing rate, the high frequency (HF) component is related to the respiratory rate, and is used as an estimate of parasympathetic activity [70].

In the provocation studies (Studies I and II), an electrocardiogram was continuously recorded during the experiments using an MP100 data acquisition unit (Biopac Systems, Inc., Goleta, CA). The recordings were digitalized, visually inspected for artefacts, and analyzed in both the time and frequency domain using ACQKnowledge III (Biopac Systems, Inc.)
and Matlab 6.0 software (Mathworks, Inc., Natick, MA). The power spectral analysis was performed by Fast Fourier Transformation (FFT).

In Study IV, short-term HRV was recorded according to standard laboratory practice with six minutes of supine rest with free breathing, one minute of paced breathing at 12 breaths/minute and four minutes of free breathing in 70° head-up position. The recording and analysis software used was developed at the Department of Biomedical Engineering and Informatics (Umeå University Hospital, Sweden) using Matlab (MathWorks Inc, Natick, MA). Data was screened for non-sinus beats and artefacts, and analyzed in the frequency domain using auto-regressive modelling.

Twenty-four hour HRV was recorded using a two-channel ambulatory Holter recorder (Braemar DL 700, Braemar Inc., Burnsville, MN). The recordings were digitalized and screened for pathological events using commercial software (Aspect Holter System, GE Healthcare, Borlänge, Sweden) and manually edited. Power spectrum analysis was performed using fast FFT. Power spectra were determined for each hour of the recording. Hourly averages of frequency domain indices were calculated over the hours between 04:00 p.m. and 08:00 a.m., a collection period that provided quality data for all subjects. Daytime HRV was calculated as an average over the hours 04:00 - 09:00 p.m. and 06:00 - 08:00 a.m. Night-time HRV was calculated as an average over the hours 10:00 p.m. - 05:00 a.m.

In all studies the recordings were analyzed using standard ranges for the very low (VLF; \( \leq 0.04 \) Hz), low (LF; \( >0.04-0.15 \) Hz), and high frequency (HF; \( >0.15-0.50 \) Hz) bands [67]. The following HRV indices were calculated: Total power in the frequency region 0.003-0.50 Hz (PTOT); power in the VLF, LF, and HF range, the normalized LF and HF power (PHFn=PHF/[PTOT-PVLF]; PLFn=PLF/[PTOT-PVLF]), and the ratio LF/HF.
Psychological measurements

Working memory and reaction time were assessed by means of the Sternberg memory test (Study I) [71]. The test was presented through a computerized slide presentation, to minimize the need for direct communication between the subject and the experimenter.

The CFFT was recorded, using the Method of Limits, to give an estimate of the subject’s level of central nervous system (CNS) arousal and current CNS processing capacity in a way that would not be much affected by practice (Study I) [72].

Personality traits, anxiety, depression, exhaustion and stress were assessed by the following questionnaire instruments (Studies III and IV):

- The State-Trait Anxiety Inventory (STAI) [73] differentiates between the temporary condition of “state anxiety” and the more general and long-standing quality of “trait anxiety”. It consists of twenty-item scales for each of the two types of anxieties. A high score refers to more trait or state anxiety.

- The Karolinska Scales of Personality (KSP) [74] is constructed to assess stable personality traits. It consists of 135 items distributed among 15 subscales, representing personality traits, which are then grouped according to five basic personality dimensions. Only the anxiety-related subscales (Inhibition of Aggression, Muscular Tension, Psychasthenia, Psychic Anxiety, and Somatic Anxiety) were used.

- The Beck Depression Inventory (BDI) [75] assesses depressive symptoms. It consists of 21 items, the sum of which indicate severity of depression.

- The Symptom Checklist-90 (SCL-90) [76] assesses patterns of current mental distress. Its 90 items are grouped into nine subscales, of which the Anxiety, Depression and Somatization subscales were used. High scores indicate higher levels of mental distress.

- The Shirom-Melamed Burnout Questionnaire (SMBQ) [77] assesses four aspects of exhaustion: Burnout, Listlessness, Tension, and Mental exhaustion. The mean of all items assesses general energetic exhaustion. High scores refer to more exhaustion.
The General Perceived Stress Questionnaire (PSQ) [78] assesses subjective perception of and emotional response to stress. Out of its 30 items, a general index is calculated, the level of which indicates the level of perceived stress.

**Definition of symptoms**

Symptoms were assessed by means of questionnaires (Studies I, II, III and IV). In all studies, an “EMF-related symptom” was defined as a symptom that the afflicted person reported to be elicited by EMF exposure. An “EMF-nonrelated symptom” (Study III) or a symptom “experienced in general” (Studies I and II) was defined as a symptom that the afflicted person reported, but did not consider elicited by EMF exposure. An individual was defined as having a symptom if the symptom was reported at least once a week.

“MP-related symptoms” were defined as symptoms reported in association with the use of MP. Symptoms attributed to one’s own MP use and those attributed to MP use by other persons were not separated. “VDT-related symptoms” were defined as symptoms reported in association with VDT-work. “EHS” was defined as having symptoms attributed to various kinds of electrical equipment. Persons with symptoms attributed to MP use were defined as having EHS if they also reported symptoms attributed to other kinds of electrical equipment. An exception was made for persons reporting both MP- and VDT-related symptoms who were defined as having MP-related symptoms, since the MP-related symptoms were predominant in this group. The classification of participants in Studies I, III and IV was based on the reported symptoms and not on the person’s own description of his or her condition. That is, individuals who, e.g., described themselves as being electromagnetically hypersensitive, but reported only symptoms associated with MP use, were assigned to the group “MP-related symptoms”.

24
The participants with EMF-related symptoms in the four studies are further referred to as:

- MP subjects: The participants with MP-related symptoms in Study I
- MP group: The participants with MP-related symptoms in Study III
- EHS group: The participants with EHS in Study III
- EHS subjects: The participants with EHS in Study IV

**Ethical considerations**

In all studies, the participation was informed and voluntary. All subjects had the possibility to withdraw from the study they participated in without giving any reasons for their withdrawal. All results were confidential, and data from single participants were identified by codes. Ethical approval of all four studies was given by the Regional Ethical Research Board at Umeå University.
Results

Effects of EMF exposure

Symptoms

The MP subjects reported more symptoms than the controls both on the day of true exposure and the day of sham exposure, but there was no significant association between RF exposure and symptoms (Study I). The AD subjects reported more symptoms than the control subjects overall in a similar manner (Study II), but no apparent association between exposure condition and symptoms was observed. The total number of symptom reports was, however, too small to allow for statistical comparison of the effects of RF exposure between AD subjects and controls. The MP subjects reported predominantly sensations of warmth on or around the ear, fatigue and cognitive symptoms (memory loss, concentration difficulties), whereas the AD subjects predominantly fatigue, headaches and itching and burning sensations of the facial skin. Six out of nine of the AD subjects with symptoms during the experiment reported also everyday MP-related symptoms, compared to two out of four in the control group. The AD subjects reporting symptoms during the exposure session did not display serum concentrations of biomarkers that deviated significantly from the rest of the subject group. No difference in perceived stress associated with exposure was observed in either study.

Physiological parameters, CFFT, cognitive function and biomarkers

No significant effects of EMF exposure were found in the provocation studies (Study I and II), neither on ANS parameters (HR, HRV, local blood flow, breathing rate, EDA), nor on biomarkers (SP, TNF-α, BDNF), CFFT, short-term memory or reaction time.

In Study I, the control subjects performed better than the MP subjects on the memory test at baseline. That is, they gave significantly more correct answers and had shorter reaction times than the MP subjects. The difference in reaction time was no longer apparent the second time the memory test was conducted. A tendency toward a lower number of
correct answers among the MP subjects remained, but the difference was no longer significant on the second day of the experiment.

The AD subjects displayed significantly higher serum concentrations of TNF R1 and significantly lower concentrations of BDNF in the baseline condition (sampling before exposure/sham exposure on day 1), differences that remained throughout the experiment (Study II). There was a tendency toward a lower SP concentration, but this difference was not statistically significant.

**Subgrouping of persons with EMF-related symptoms**

**Symptom prevalence**

The prevalence of EMF-related and EMF-nonrelated symptoms in the studies I, II, and III are shown in Table 1. In all studies where “case” subjects were compared with controls, they reported more EMF-nonrelated symptoms than did the control subjects. This was so not only for subjects with EMF-related symptoms (Study I and III), but also for the AD subjects in Study II. In Study III, the EHS group reported higher prevalence of all symptoms not related to EMF than any of the two reference groups. The MP group also reported a higher prevalence of most EMF-nonrelated symptoms than the two reference groups, but less symptoms than the EHS group, with the exception of sensations of warmth behind/around and on the ear. The MP groups in Study I and III were fairly similar with respect to prevalence of EMF-nonrelated symptoms.

The most commonly reported MP-related symptoms varied somewhat between study groups. Among the MP subjects in Study I, the most common symptoms were fatigue, memory loss, concentration difficulties, and warmth sensations on and behind the ear. Among AD subjects the most common symptoms were sensations of warmth on or around the ear. The AD subjects did not differ significantly from the control subjects with respect to MP-related symptoms; however, the control subjects reported more sensations of warmth on or around/behind the ear than the AD subjects. The symptom reports of the MP subjects in Study I were similar to that of the MP group in Study III (somatosensory symptoms from the head were the most common), but the prevalence of headaches and general discomfort was higher in Study III. EMF-related symptoms were found also in the population-
based reference group in Study III. The symptoms most commonly reported were warmth sensations on or behind/around the ear, burning skin, headaches, and fatigue.

The EHS subjects in Study IV reported fewer EMF-related symptoms (mean number of symptoms=4.4, S.D. 1.9) than the EHS group in Study III (mean 9.7, S.D. 3.3). Dizziness, general discomfort, and tingling/tightness of the facial skin were most commonly reported.

Among the MP subjects in Study I, a tendency was observed toward an increased number of MP-related symptoms with a longer time of MP use (in years), longer calling times per day, and a larger number of calls per day. Symptoms were also reported to occur mostly at long calls. The MP subjects also reported generally longer calling times, a higher number of calls and longer MP use than the controls (mean, MP: 12.3 years; mean, controls: 8.9 years). In contrast, no such associations were observed in the MP group in Study III, neither with respect to calling times nor with respect to number of calls or years of MP use. There was also no apparent association between the number of EMF-related symptoms and the number of years for which the symptoms had been present.
Table 1. Percentage of subjects with self-reported symptoms occurring at least once a week. Symptoms reported in general are not necessarily attributed to EMF exposure while EMF-related symptoms are. EMF-related symptoms may be attributed to exposure from mobile phones, visual display terminals or electrical equipment in general. (I, II, III refer to study number 1-3.)

<table>
<thead>
<tr>
<th></th>
<th>MP subjects (I) (n=20)</th>
<th>MP control (I) (n=20)</th>
<th>AD subjects (II) (n=15)</th>
<th>AD control (II) (n=15)</th>
<th>MP group (III) (n=45)</th>
<th>EHS group (III) (n=71)</th>
<th>PB group (III) (n=106)</th>
<th>C group (III) (n=63)</th>
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<tr>
<td></td>
<td>General EMF</td>
<td>General EMF</td>
<td>General EMF</td>
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<td>General EMF</td>
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<td>0 0</td>
<td>0 0</td>
<td>18 27</td>
<td>42 75</td>
<td>13 7</td>
<td>11 0</td>
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<td>5 0</td>
<td>7 7</td>
<td>0 7</td>
<td>29 73</td>
<td>77 92</td>
<td>11 9</td>
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<td>5 0</td>
<td>20 0</td>
<td>0 0</td>
<td>36 42</td>
<td>68 81</td>
<td>18 10</td>
<td>13 0</td>
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<td></td>
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<td>13 0</td>
<td>0 0</td>
<td>31 22</td>
<td>49 61</td>
<td>12 3</td>
<td>10 0</td>
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<td>20 0</td>
<td>7 0</td>
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<td>75 80</td>
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<td>7 0</td>
<td>33 20</td>
<td>73 65</td>
<td>30 4</td>
<td>21 0</td>
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<td>Warmth behind/around ear</td>
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<td>0 0</td>
<td>7 13</td>
<td>7 40</td>
<td>47 84</td>
<td>41 66</td>
<td>4 12</td>
<td>0 0</td>
</tr>
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<td>Warmth on ear</td>
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<td>0 0</td>
<td>0 0</td>
<td>13 0</td>
<td>40 40</td>
<td>82 80</td>
<td>39 67</td>
<td>5 19</td>
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<td>Burning skin</td>
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<td>5 0</td>
<td>27 0</td>
<td>0 7</td>
<td>36 64</td>
<td>62 90</td>
<td>12 20</td>
<td>0 0</td>
</tr>
<tr>
<td>Tingling/tightness</td>
<td>25 15</td>
<td>0 0</td>
<td>27 0</td>
<td>0 7</td>
<td>18 51</td>
<td>54 79</td>
<td>3 4</td>
<td>2 0</td>
</tr>
<tr>
<td>Itching face</td>
<td>na na</td>
<td>na na</td>
<td>47 7</td>
<td>0 0</td>
<td>na na</td>
<td>na na</td>
<td>na na</td>
<td>na na</td>
</tr>
<tr>
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<td>0 0</td>
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<td>Other symptoms</td>
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<td>13 0</td>
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<td>na na</td>
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</tr>
</tbody>
</table>

ANS activity

No statistically significant differences in baseline (registrations before exposure/sham exposure on day 1) heart rate, HRV, breathing rate, or electrodermal activity between MP/AD subjects and controls were encountered in either of the two provocation studies. There was also no difference in baseline CFFT between MP subjects and controls (Study I). The MP subjects displayed significantly higher LF power during the CFFT tests and the memory tests than did the controls, as well as significantly lower HF power, resulting in a higher LF/HF ratio (Figure 3).

In the investigation of 24-h HRV (Study IV), the main finding was a general increase in HFn at follow-up with a statistically significant difference between day-time HFn at follow up and at the initial measurement. Two EHS subjects displayed a night-time increase in HFn at follow-up, whereas none of the subjects displayed a difference between daytime and night-time values at the initial measurement. Heart rate and all other HRV measures were essentially unchanged. The short-term recordings revealed normal responses to paced breathing and tilt-test. Three out of five subjects displayed high overall HRV with high LF values and comparatively low HFn values compared to an age-matched control group (Figure 4a, b). The other two subjects displayed lower overall HRV with values more similar to the average values of the control group. The differences between individuals were large both for 24-h and short-term recordings.
Figure 3. Ratio of the low (LF) and high (HF) frequency heart rate variability components of subjects with MP-related symptoms and control subjects during the provocation experiment (Study I), indicating sympathovagal balance. Group means and 95% confidence intervals (bars) for case and control groups are shown (▲ = MP subjects, RF exposure; ■ = MP subjects, sham exposure; Δ = controls, RF exposure; ○ = controls, sham exposure). Duration of the whole provocation experiment: approximately 60 min, duration of single test sessions: approximately 10 min, duration of exposure: 30 min.

Psychological aspects

Both groups with EMF-related symptoms investigated in Study III (MP and EHS) reported on average higher levels of anxiety, depression, exhaustion and stress than the reference groups; they also reported differences related to personality traits (Table 2). The differences between the total group with EMF-related symptoms and the population-based reference group were statistically significant for the global mean and all subscales of the SMBQ, the subscales Muscular Tension, Psychasthenia, and Somatic Anxiety from the KSP, the BDI, all subscales from the SCL-90, and the STAI Trait subscale, but not for the STAI State subscale, the PSQ and the KSP subscales Inhibition of Aggression and Psychic Anxiety.
When the total group with EMF-related symptoms was compared with the symptom-free control group, the difference was no longer significant for the STAI Trait subscale, the KSP Psychasthenia subscale and the SMBQ Tension subscale. The average scores of the control group differed little from those of the population-based group for most variables.

The EHS group scored higher than the MP group on all scales except for the STAI, the PSQ, the KSP subscale Psychic Anxiety, and the SMBQ Tension subscale. However, only the differences for the Somatization subscale of the SCL-90 and the Listlessness subscale of the SMBQ were statistically significant. The EHS group differed from the reference groups to a higher extent than did the MP group.

In the pilot study, Study IV, the data on stress, anxiety and exhaustion were highly variable. The scores of three of the EHS subjects were similar to those of the population-based group in Study III. The scores of the fourth subject were comparable with those of the EHS group in Study III, and the scores of one subject exceeded those of the EHS group.
<table>
<thead>
<tr>
<th>Questionnaire instrument</th>
<th>Study III</th>
<th>Study IV</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MP (n=45)</td>
<td>EHS (n=71)</td>
</tr>
<tr>
<td>STAI</td>
<td></td>
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<tr>
<td>Trait</td>
<td>38.9 (13.0)</td>
<td>38.8 (12.3)</td>
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<tr>
<td>State</td>
<td>34.6 (12.5)</td>
<td>34.6 (14.1)</td>
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<td>KSP</td>
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<tr>
<td>Inhib. of Aggression</td>
<td>23.2 (6.1)</td>
<td>23.6 (5.2)</td>
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<td>Muscular Tension</td>
<td>18.9 (6.7)</td>
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<td>Psychasthenia</td>
<td>22.7 (7.8)</td>
<td>24.4 (5.4)</td>
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<td>Psychic Anxiety</td>
<td>19.7 (7.0)</td>
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<td>Somatic Anxiety</td>
<td>17.5 (6.5)</td>
<td>19.4 (6.6)</td>
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<tr>
<td>BDI</td>
<td>9.59 (9.6)</td>
<td>10.56 (9.3)</td>
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<tr>
<td>SCL-90</td>
<td></td>
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<tr>
<td>Anxiety</td>
<td>0.66 (0.72)</td>
<td>0.76 (0.85)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.86 (0.54)</td>
<td>0.94 (0.46)</td>
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<td>Somatization</td>
<td>0.90 (0.74)</td>
<td>1.3 (0.93)</td>
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<td>SMBQ</td>
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<td>Global</td>
<td>3.52 (1.74)</td>
<td>3.99 (1.48)</td>
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<td>3.52 (1.88)</td>
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<tr>
<td>Listlessness</td>
<td>1.77 (0.52)</td>
<td>2.06 (0.43)</td>
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<td>Tension</td>
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<td>3.38 (0.96)</td>
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<td>Mental Exhauseation</td>
<td>1.77 (0.52)</td>
<td>1.94 (0.47)</td>
</tr>
<tr>
<td>PSQ</td>
<td>0.56 (0.22)</td>
<td>0.56 (0.17)</td>
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</tbody>
</table>

MP: Subjects reporting mobile phone-related symptoms
EHS: Subjects reporting electromagnetic hypersensitivity
PB: Population based reference group
C: Control group without EMF-related symptoms
S1-5: Subjects 1-5
na: not asked
Discussion

Effects of exposure

Symptoms

In both provocation studies, a larger number of subjects experienced symptoms during exposure than during sham exposure. However, a considerable number of subjects reported symptoms during sham exposure only, or in both conditions, and the difference in the number of symptom reports between the exposure conditions was small. The somewhat higher number of symptom reports during exposure than during sham exposure in Study I may be partly associated with the fact that more subjects received exposure on day 1 than on day 2. A higher degree of anticipatory stress is probably to be expected during the first experimental session than on the second, and this may have worsened symptoms. An association between the assumption of being exposed and triggering of symptoms, regardless of exposure condition, has been observed [25]. Open provocation has also been observed to trigger symptoms more effectively than blind provocation, which has been interpreted as an effect of anticipation [79].

The failure to demonstrate an association between exposure and symptoms are in line with most previous findings [27, 39]. However, most MP subjects reported symptoms during the experiment, which were similar to those that they reported in association with MP use in everyday life. If these symptoms may be provoked in the laboratory by perceived stress, the role of stress in the provocation of these symptoms in everyday life should also be considered.

The comparison between provocation studies is complicated by the fact that different studies have used different outcomes. Specific symptoms have been asked for by the experimenters, or the subjects have been asked to report any symptom [27, 35, 39]. The evaluation of symptom reports is further complicated when field perception is assessed simultaneously, given the observed tendency of individuals with EMF-related symptoms to report more symptoms in association with perceived exposure [39, 79].
Physiological parameters, CFFT and cognitive function

The absence of an effect of RF exposure on ANS activity, CFFT, reaction time or short-term memory in subjects with and without MP-related symptoms are in line with most previous findings, although EEG changes and improved cognitive performance during RF exposure have recently been reported [27, 39, 50, 80, 81]. Wiholm et al. [81] reported enhanced spatial memory during exposure in subjects with MP-related pain or discomfort in the head, but not in control subjects. In Study I, an improvement in cognitive function was found among the MP subjects, but not among the control subjects; however, as the change was associated only with the number of performed tests and not with exposure condition, the finding was considered a practice effect.

Biomarkers

Elevated plasma concentrations of SP and vasoactive intestinal peptide together with increased skin wheal responses have previously been reported in AD subjects after exposure to an MP [82]. The skin symptoms reported by people with MP-related symptoms do to some extent resemble those seen in AD (e.g., sensations of tingling/tightness or burning of the facial skin, itch, and erythema); therefore it was of interest to examine whether the skin symptoms seen in AD and those seen in MP-related symptoms might share underlying mechanisms. People with AD also tend to be extra susceptible to exposure to physical factors in the indoor environment [83]. Consequently, they may be assumed to be more sensitive to RF exposure. However, in Study II, isolated RF exposure did not affect serum concentration of SP, nor did it affect the concentrations of TNF-α or BDNF. The difference between subjects with and without AD in baseline serum concentration of the investigated biomarkers may be explained by an inflammation in AD, since the biomarkers are known to be sensitive to inflammation.

The differences between Study II and the study by Kimata et al. [82] should be noted. In Study II, the subjects were exposed via indoor base station antennas and not via an MP. The order of the exposure condition (exposure/sham exposure) in Study II was randomized to avoid effects of anticipatory stress, since skin symptoms may be provoked by stress [83]. Furthermore, all concentrations were measured in serum instead of
in plasma, since serum analysis has given more reliable results in other projects performed at the same laboratory [84].

The finding that the control subjects in Study II actually reported more sensations of warmth during MP calls than the AD subjects may partly be explained by the fact that people with AD regularly experience a variety of skin symptoms to an extent that may mask similar symptoms occurring during MP calls.

Taken together, our observations do not support the hypothesis that exposure to MP-like RF electromagnetic fields will provoke any of the symptoms registered or affect ANS activity, CFFT, cognitive function or serum concentrations of SP, TNF-α or BDNF.

**Subgrouping of persons with EMF-related symptoms**

Persons with EMF-related symptoms are known to constitute a very heterogeneous group [29]. Observations from Study I indicated differences between the MP subjects of this study and EHS subjects in previous studies performed in the same laboratory with respect to symptom picture, but also with respect to attitudes and behaviour [55, 56, 85]. Similar observations have been made by others [43]. Earlier, studies have observed differences between persons with EHS and persons with VDT-related symptoms, with respect to psychological aspects, medical prognosis and the impact of EMF-related symptoms on working capability and social life [44, 45, 86]. The authors of these studies considered the differences profound enough to propose that EHS and VDT-related symptoms should be regarded as distinct subgroups of EMF-related symptoms [25, 44, 45]. With reference to this, the question was raised, if MP-related symptoms may constitute another subgroup of EMF-related symptoms, possibly more similar to VDT-related symptoms than to EHS.

**Symptom prevalence**

Even though there was considerable interindividual variation in symptoms, a difference in symptom picture between those with MP-related symptoms and those with EHS was apparent. Among the MP subjects in Studies I and II, somatosensory symptoms located to the head predominated (sensations of warmth on or around the ear, headaches, burning sensations or tingling/tightness in the facial skin),
together with general discomfort and cognitive disturbances. Among the participants with EHS in Studies III and IV, neurasthenic symptoms (dizziness, fatigue, sleep disturbances) were more frequent, even though they also reported somatosensory symptoms. Similar differences with respect to symptoms have been observed previously [29]. As a result, persons with MP-related symptoms apparently resemble the previously described group with VDT-related symptoms in that the individuals report less neurasthenic symptoms than persons with EHS.

In Studies I, II and III, the participants with EMF-related symptoms also more often reported symptoms which they did not associate with EMF exposure than the reference/control groups. The prevalence of EMF-nonrelated symptoms in the EHS group in Study III was very high; most symptoms were reported by at least 40% of the participants. Several of the symptoms assessed, e.g., fatigue and headaches, are unspecific and common in the general population [87]; however, the reported numbers are still conspicuous. Group differences with respect to age and sex may explain part of the difference in symptom reports, however not all.

The similarity between the pictures of EMF-nonrelated and EMF-related symptoms reported raises the question whether it might be difficult for afflicted individuals to discriminate between EMF-related and EMF-nonrelated symptoms. This may be more difficult the more unspecific the symptoms are and the more EMF sources that are assumed to provoke symptoms.

Other health-related factors

The prevalence of illnesses other than EMF-related symptoms reported by the EHS group was higher than that of the other groups (48% of the EHS group, 18% in the MP group and 26% in the population-based reference group). This may account for some of the difference in EMF-nonrelated symptoms between the groups. Skin symptoms were frequently reported, but the prevalence of skin disease was not higher in any of the groups with EMF-related symptoms. This is in line with previous observations, even if results are not concordant between studies [31, 45]. The prevalence of other diseases also differs between studies, which may partly be due to differences in subject selection. Patient populations, recruited via patient support groups, primary care clinics or specialist departments may be assumed to exhibit both somatic and psychiatric comorbidity to a higher extent than non-patient populations [88, 89].
Allergy was more frequently reported by the EHS group (65%) than by the reference group, whereas the MP group (30%) did not differ much from the reference group (40%) in this aspect. A high prevalence of self-reported allergy among persons with EHS has been observed previously, but it is uncertain to what extent the reports represent allergy or annoyance [31, 90]. People with EHS also report more annoyance from environmental factors other than EMF, such as noise and indoor air factors, compared with controls [22]. Moreover, a higher CFFT compared with controls, and an increased response to flickering light as assessed by visual evoked potentials has been observed in EHS subjects [55, 85]. In contrast, in Study I, MP subjects did not display higher CFFT compared with controls [91]. In Study III, the EHS group reported more symptoms related to TV (68%) and fluorescent lighting (80%) than the MP group (TV: 18%, fluorescent lighting: 22%) and the reference group (TV: 18%, fluorescent lighting: 4%). Both are, apart from being perceived as sources of EMF exposure also sources of flickering light [57]. It seems that persons with EHS may be bothered by various environmental factors to a higher extent than persons with MP-related symptoms.

**Age and sex distribution**

The participants with MP-related symptoms in Studies I and III were younger than those with EHS, and the proportion of men was higher. Epidemiological studies of EHS generally report a higher proportion of women [31, 32, 45, 90]. A survey among mobile phone users in Norway and Sweden indicated that, although female gender was considered a risk factor for having MP-related symptoms, the proportion of men might be higher in this group than among persons with EHS [37]. At the time of the investigation MP use was, however, considerably more common among men than among women. There are, to my knowledge, no investigations of more recent date assessing the prevalence of MP-related symptoms specifically, but the sex distribution in some studies with smaller numbers of participants indicates that there may actually be a difference between EHS and MP-related symptoms in this respect [44, 45, 91-93].
In Studies I and III, there was a tendency toward higher reported psychosocial workload as well as a higher proportion of white-collar workers, and more hours of VDT-work among participants with MP-related symptoms when compared with controls/referents. The EHS group resembled the MP group with respect to occupation and hours of VDT-work, but resembled the population-based reference group with respect to reported psychosocial workload. The differences are small, but taken together they indicate that there may be differences between the groups with respect to work situation. However, these differences refer to the subjects who were actually working, which in the EHS group was only half of the group.

A large proportion of the EHS group in Study III reported either being on sick leave or having received disability pension; a notably larger proportion than in the MP group. Among these, 9% reported that they were on sick leave due to their EMF-related symptoms, and 30% reported having ceased work due to their EMF-related symptoms. The corresponding numbers in the MP group were 5% and 25%, respectively. These reports refer to the belief of the individuals in question, as IEI, EMF-related symptoms, or EHS are not recognized diagnoses in Sweden, and consequently do not qualify as reasons for sickness compensation or disability pension. In accordance with the differences in consequences of EMF-related symptoms for the working capability, 84% of those reporting EMF-related symptoms in the population-based group and 78% of the MP group, but only 20% of the EHS group reported that although they might be annoying, the EMF-related symptoms did not affect their daily life. Twenty-four percent of the EHS group reported avoiding most social situations due to the risk of being exposed, and thereby provoking or aggravating their symptoms. Substantially compromised working capability among persons with EHS has previously been observed; however, the numbers vary between study populations. In samples recruited via EHS support groups, percentages as high as 70-80% have been reported [44, 94]. This indicates that persons with MP-related symptoms resemble persons with VDT-related symptoms more than persons with EHS, with respect to the social and work-related impact of their EMF-related symptoms [42, 45].

The results indicate that persons with EHS are more disabled by their condition than persons with MP-related symptoms with respect to both working capability and social life. Persons with EHS may also be more
easily annoyed by environmental factors in general than persons with MP-related symptoms.

**ANS activity**

ANS activity in provocation experiments

The elevated LF/HF-ratio, indicating shift of the ANS activity toward sympathetic predominance, observed in the MP subjects in Study I during functional tests (CFFT, memory and reaction time) may be interpreted as a sign of elevated sympathetic reactivity to cognitive stress. The fact that the difference between MP subjects and controls was larger during the memory test than during the CFFT test supports this view. Whereas the CFFT test assesses primarily perception threshold as a measure of attention, the memory test is a test of performance. Consequently, it may be assumed that the perceived stress of the subjects was higher during the memory test. The interpretation of the HRV findings as a marker of perceived stress is supported by previous observations of an association between stress and HRV changes toward sympathetic predominance, both under laboratory conditions and in daily life [95, 96].

The MP subjects did not differ from the control subjects with respect to physiological parameters in the resting condition, an observation that is different from those in previous studies of EHS subjects [55, 56]. EHS subjects have been observed to display significantly higher values of HR, breathing rate, and EDA, as well as an elevated LF/HF-ratio not only during functional tests, but also during rest. This was interpreted as a sign of general sympathetic predominance and hyperresponsiveness to sensory and cognitive stimulation [55, 56]. It seems that there may be a difference between people with EHS and people with MP-related symptoms with respect to ANS activity. While EHS subjects have displayed signs of a general shift of the sympathovagal balance toward sympathetic predominance, MP subjects have displayed only an enhanced reactivity to cognitive stress.

Differences in ANS activity in a laboratory setting may also reflect differences in the appraisal of the test situation. It is possible that EHS subjects would experience more stress in the laboratory than MP subjects. As persons with EHS generally experience both a higher number of symptoms and symptoms related to a higher number of EMF sources than persons with MP-related symptoms, EHS subjects
may be more stressed at the prospect of being exposed and by the unfamiliar laboratory environment that is possibly perceived as containing many EMF sources (although this was not the case). MP subjects may be assumed to experience less distress than EHS subjects in an environment containing electrical equipment other than MP, since they attribute their symptoms to MP only.

The indications of a difference in baseline autonomic activity between persons with MP-related symptoms and persons with EHS are to some extent supported by the different symptom pictures. Persons with EHS reporting a larger number of symptoms and symptoms from a larger number of organ systems than persons with MP-related symptoms, and those with EHS also more commonly report dizziness, fatigue and sleeping disorders, complaints that may be associated with ANS derangement [97].

**Follow-up of 24-h HRV in EHS**

The general tendency toward increased HF n at follow-up for all subjects may be interpreted as a sign of increased parasympathetic activity. In contrast with the initial recordings (2001), when the night-time increase in parasympathetic activity expected in healthy individuals was absent in all EHS subjects, two of the subjects displayed increased night-time parasympathetic modulation at follow-up. For the other three, signs of decreased night-time parasympathetic modulation were still present. A night-time HRV pattern indicating parasympathetic withdrawal has been observed as an effect of perceived stress, and parasympathetic withdrawal has been suggested as one of the mechanisms through which stress disrupts sleep [98]. This suggestion is of interest, as sleeping disorders and fatigue are commonly reported in EHS. However, in Study IV, no apparent association between reports on perceived stress and indications of decreased parasympathetic or increased sympathetic activity could be observed.

The number of subjects in Study IV was too small to allow general conclusions about persons with EHS, especially as the study contained no control group, and as the interindividual variation of the HRV in persons with EHS is not known. However, the indications of improved sympathovagal balance with time observed in this pilot study, together with the fact that all subjects reported experiencing less symptoms at follow-up, merits further investigation, especially as there is disagreement concerning the time course of EHS.
Psychological aspects

The results from Study III - with the EHS group overall reporting the highest levels of anxiety, depression, exhaustion, and stress and the MP group reporting levels between the EHS group and the reference groups - support the idea that groups with EMF-related symptoms that differ with respect to the EMF sources to which their symptoms are attributed, differ also with respect to other factors. The degrees of anxiety (as assessed with the SLC-90), depression and exhaustion reported by the participants with EMF-related symptoms fall between those of the general population and those observed in patients with depression or psychosomatic disorders; corresponding with observations in other types of IEI [99, 100]. It has previously been pointed out, that although patients with EHS report considerable distress, they do not necessarily have psychiatric diagnoses [53]. Substantial psychiatric comorbidity in subjects with IEI has been reported, but as with the reports on other individual risk factors, results differ considerably between studies [101]. It is also difficult to separate psychiatric comorbidity that may have predisposed for the development of IEI from the effects of long-term illness.

The results from the Somatization subscale of the SCL-90 are not easily interpreted since this scale is composed of questions about various somatic symptoms and persons with EHS often base the assumption that they are hypersensitive on the fact that they experience somatic symptoms. Some of the items of the Somatization subscale refer to symptoms - such as e.g., fatigue, dizziness, and shortness of breath - that might be explained by the ANS derangement observed in persons with EHS. Moreover, both depression and anxiety, which are more prominent in both groups with EMF-related symptoms than in the reference groups, are associated with somatic symptoms [99, 102]. This association may be interpreted both as a tendency of psychological distress to increase somatic complaints, and as a tendency of somatic complaints to increase psychological distress.

As to perceived stress the MP group reported levels with or higher than the EHS group. This was expected from observations from Study I, where the MP subjects reported not only high numbers of MP calls per day and long calling times, but also long working hours and frequent feelings of being overloaded with work, although the estimation of psychosocial workload did not differ between the MP subjects and the controls. The MP subjects' poorer performance on the short-term
memory test compared to controls should probably be discussed in this context. As the difference was statistically significant only the first time the test was performed, that is, it disappeared with practice; it probably did not reflect a difference in baseline cognitive capacity between the MP subjects and the controls. It is likely that the effect of anticipatory stress at the prospect of being exposed to an agent that might elicit unpleasant symptoms was stronger in the MP subjects. Allocating attention to perceived exposure may be assumed to impair working memory. However, an effect of a more general stress than that experienced in this particular experimental situation is also possible. The MP subjects reported both concentration difficulties and memory loss that was not related to MP use to a higher extent than did the controls, and cognitive impairment is a well-known effect of stress [103]. This, in combination with the MP subjects’ higher sympathetic response to the CFFT test and the cognitive test suggests that the question of general perceived stress should probably also be addressed in the discussion of MP-related symptoms. The reports on cognitive symptoms by the MP subjects in Study I correspond well with those by the MP group in Study III, where a slight tendency toward higher psychosocial workload was observed compared with the reference groups. An association between EMF-related symptoms and psychosocial workload has previously been suggested [104, 105].

The increased responsiveness to physical and cognitive stimuli, and the general annoyance attributed to environmental factor observed in persons with EMF-related symptoms has been suggested to indicate sensitization [106]. Sensitization is described as the augmentation of the response to sensory input following repeated exposure, e.g., the opposite of habituation and may occur both at the neuronal level and at the cognitive level [107]. For pain processing, the mechanisms of both central and peripheral sensitization are reasonably well established, whereas the description of cognitive sensitization, suggested to arise from sensitization of neurons in limbic structures, is more speculative, due to the multiple neural and psychological processes involved. [108-110]. Both neuronal and cognitive sensitization have been suggested as underlying factors in multiple chemical sensitivity, another subtype of IEI, as well as in unspecific health complaints in general [107, 111]. Neuronal sensitization may explain ANS hyperresponsiveness to physical stimuli, increased levels of annoyance by environmental factors, and increased pain sensitivity [106, 112]. Cognitive sensitization may lead to increased attention to somatic symptoms and unpleasant sensations in
This may result in a tendency to interpret normal physiological signals as threatening and, in turn, in the amplification of symptoms. The increase in attention may also be directed toward information related to fears of the sensitized person (e.g., fear of unpleasant symptoms or of exposure to EMF), especially in persons with a high background level of anxiety. It has further been proposed that cognitive sensitization may be an underlying mechanism in anxiety and depression in itself. The symptom picture commonly observed in EHS, with several unspecific symptoms arising from multiple organ systems and provoked by a wide range of exposure sources, together with high levels of anxiety further speaks in favour of sensitization [114]. The observed differences in physiological and psychological aspects between persons with EHS and persons with MP-related symptoms, suggests that the two groups may differ also in this respect.

When the questionnaires used in Studies III and IV were examined on the level of single items, additional differences between the MP and EHS groups appeared. The MP group was high on items assessing tension, work-related stress, and perceiving having too much to do, whereas the EHS group was high on items assessing unspecific anxiety and worry. The difference may be explained by fact that the participants in the MP group were occupationally active to a higher extent than those of the EHS group; however it may also indicate different cognitive styles. Worry has been pointed out as significant for the development and maintenance of unspecific somatic symptoms in general. Perseverative cognition - e.g., worry - may serve as a mediator between the acute stress response and prolonged, pathogenic stress by prolonging the stressor itself [114]. Through this mechanism, worry may also lead to cognitive sensitization, with increased attention both to somatic symptoms and information relating to the perceived causes of these symptoms [116]. It has further been suggested that worry may have detrimental effects on the perceived coping ability of the worrying individual. Differences related to coping ability have been observed between persons with EHS and persons with VDT-related symptoms [86]. Coping has, to my knowledge, so far not been investigated in persons with MP-related symptoms and this might therefore be of interest for future research.

The variation within groups was large; all groups consisted of both individuals that reported very low and individuals that reported very high levels of the assessed aspects. This is further illustrated by the results from Study IV, in which some EHS subjects, although they were classified as EHS on the basis of their symptom attribution, actually
scored lower than the reference group in Study III; whereas one subject gave high scores, similar to those observed in “burnout” patients [117]. This emphasizes the heterogeneity of both the MP and the EHS groups, and points to the need for a case-by-case approach in the management of patients with EMF-related symptoms. Taken together, the results indicate noticeable distress among people with EMF-related symptoms and group differences between persons with MP-related symptoms and persons with EHS in this respect.

**Methodological considerations**

**Selection of subjects**

With the exception of the reference groups in Study III, the study participants were not randomly selected, and they may thus not straightforwardly be regarded as representative samples of any of the groups “people with EMF-related symptoms”, “people with MP-related symptoms” or “people with EHS”. Those with the most severe symptoms are less likely to voluntarily take part in a study involving exposure that may be assumed to elicit symptoms. This refers to the Studies I and II, but also to Study IV, since the crucial factor is the perception of exposure and not the exposure per se.

In the two provocation studies, different criteria were used for the selection of control subjects. In Study I, the controls were selected with the requirement that they did not experience symptoms related to MP use, whereas in study II the primary selection criterion was absence of atopic disease, whereas presence or absence of MP-related symptoms was not questioned in the recruitment. Consequently, the control group in Study II may have encompassed subjects that might as well have belonged among the MP subjects in Study I.

In Study III, the number of questionnaires was large, and will have required considerable time for completion, limitations that may have affected which subjects that chose to participate. Some people may also have been offended and chose not to participate because the main part of the questionnaire set included questions dealing with psychological factors and not with EMF exposure. Since the group of people experiencing EMF-related symptoms beforehand is known to be heterogeneous, the possible non-representativeness of study participants will complicate the interpretation of the results.
The EHS subjects in Study IV were recruited among the participants of a previous study, and chosen for the reason that they were among those who displayed the most pronounced signs of decreased night-time parasympathetic activity. As such signs were not found among all subjects in the initial study; the subjects in Study IV may not be regarded as representative for persons with EHS in general.

**Exposure in the provocation studies**

Indoor base station antennas were used as the exposure source instead of an ordinary mobile phone, to achieve the greatest possible control over the exposure and to avoid confounding factors such as heating and the low frequency magnetic field emitted from handheld GSM units. The energy deposition in the head during an MP call is known to differ between different MP due to differences in antenna configuration [118]. However, no clear relation between symptom prevalence and the localization of the RF exposure has been observed, although a weak correlation between symptoms and SAR has been seen [118]. Since neither the mechanisms through which RF exposure from MP would affect the body, nor the target tissue have been identified, it seems appropriate to expose the whole area in which ordinary MP may deposit the RF energy. The exposure is clearly different from the combination of RF and low frequency exposure, and temperature increase that is present during an ordinary MP call, but makes it possible to draw conclusions about the effect of isolated RF exposure in a way that the results from a combined exposure would not. The difference between the assessment of the effects of RF exposure and the assessment of the effects of MP use should be noted.

The exposure setups used in the provocation studies conducted so far differ widely. Several studies have used an MP held to the ear by hand or with a rubber cap [48, 119, 120]. The only exposure parameter reported in these studies was the maximum SAR in 1 or 10 g tissue. This may be compared with the elaborate exposure setup described by Schmid et al. [121] and used by Hillert et al. [122] consisting of a low-weight, stacked micro patch antenna fixed on a headset worn by the subjects, and with exposure signals simulating the EMF induced in the head during a conversation with a GSM handset. Such a system exposes all tissues that are exposed during real-life MP calls and takes into account differences in phone design, phone position and head anatomy. Apart from exposure setups, exposure levels and exposure times also differ.
considerably between studies. Hillert et al. [12] used a peak spatial SAR of the gray matter averaged over a cube of 1 g of 1.8 W/kg during 3 h of exposure, whereas most other studies report SAR values below 1 W/kg, and exposure times between 15 and 30 min. The variation between the exposure setups, SAR values and distribution, and exposure times used in different studies should be noted when comparing the results of the studies.

**Twenty-four hour versus short-term HRV recordings in EHS**

Despite the variation between individuals, the 24-h and short-term HRV recordings in Study IV were similar for each subject, in that the three subjects with a high overall 24-h HRV at follow-up also displayed a higher overall HRV in the short-term recordings. This may be interpreted as both recordings indicating elevated sympathetic activity in these individuals. Moreover, the 24-h HRV pattern of the three subjects with a high overall HRV at follow-up were similar to that of their initial recordings, with signs of decreased night-time parasympathetic modulation.

The two individuals with short-term HRV more similar to that of the control group also displayed 24-h HRV changes at follow-up indicating increased night-time parasympathetic modulation toward a circadian HRV pattern more similar to that expected in healthy subjects.

As all subjects reacted normally to paced breathing and tilt test, the deviations in the circadian rhythm (e.g., the signs of parasympathetic withdrawal) observed in EHS subjects may not necessarily show in these tests. Short-term HRV recording may consequently be of limited value as a method for clinical investigation of EHS patients, on the basis of the presence of EMF-related symptoms alone.

Normative values for HRV, as well as data on the reliability and the stability of HRV over time are still scarce. For short-term recordings, the day-to-day variation is considerable; however, it is still small compared with the variation between individuals [123]. The reliability is improved by performing measurements under controlled circumstances. Twenty-four hour HRV is less well evaluated, but there are indications that it may be fairly stable over time [124, 125]. It should, however, be noted that much of the available data refer to patients with conditions where HRV is known to be decreased, e.g., diabetes mellitus or cardiovascular
disease. HRV is further known to decrease with age, especially the HF component, and to vary between sexes [126].

Due to the size of the interindividual HRV differences, large sample sizes are needed in order to detect differences between groups. Depending on the HRV indexes of interest, samples sizes of up to 100 have been suggested [123]. The sample of five individuals examined in Study IV is consequently far too small to allow any firm conclusions other than that there is considerable variation between person with EHS, with respect to both short-term and 24-h HRV. However, the indication of changes toward increased parasympathetic activity is unlikely to be only an effect of time or of random variation, and would be of interest for further study.
Practical implications

The suggestion that persons with EMF-related symptoms who attribute their symptoms to different EMF sources may differ with respect to other factors than symptom attribution is not new [44]. The results presented in this thesis provide further support for this view, as they indicate differences between persons with MP-related symptoms and persons with EHS with respect to prevalence and severity of both EMF-related and EMF-nonrelated symptoms, ANS function, and personality traits, anxiety, depression, exhaustion and stress. These differences are likely to be of importance for the outcome of medical treatment and remedial activities, and should therefore be considered in both health care and general public settings.

The differences between subtypes of EMF-related symptoms are also relevant in a research perspective. The heterogeneity among persons with EMF-related symptoms has repeatedly been pointed out as an obstacle when conducting research in this area, and the differences in selection criteria between studies complicate the interpretation of the results. Inclusion criteria vary widely between studies, and mostly, participants with different symptom attribution have not been separated. Other examples of selection criteria are that the subjects experience headaches when using an MP, or that the subjects report symptoms in open provocation [92, 122]. Study groups will also differ depending on how the question of “sensitivity” is assessed. Individuals with EMF-related symptoms may or may not label themselves as “sensitive”, and consequently, inclusion based on symptom reports will result in a different study group compared with inclusion based on reported “sensitivity”. Given that these groups differ with respect to other factors than symptom attribution, or the adoption of the label “sensitive”, this will affect the results. Moreover, patient samples and samples recruited from support groups are likely to have more severe symptoms than samples recruited at workplaces or from the general population. Different populations will most likely differ not only with respect to number and severity of EMF-related symptoms, but also with respect to other factors. Careful consideration of selection criteria is consequently recommended in future research.
Conclusions

- There were no effects of exposure to MP-like RF electromagnetic fields at the levels used in our studies on symptoms, physiological parameters, critical flicker fusion threshold, cognitive function or biomarkers.

- Persons with MP-related symptoms differ from persons with EHS with respect to symptoms, self-reported personality traits, anxiety, depression, exhaustion, and perceived stress. However, there is considerable heterogeneity within both groups.

- There are indications of a difference in ANS activity between persons with EHS and persons with MP-related symptoms. Specifically, persons with MP-related symptoms exhibit normal resting values but signs of enhanced sympathetic responsiveness to functional tests, in contrast to previously observed signs of a general sympathetic predominance in persons with EHS.

- Persons with EHS may improve with time, with respect to symptoms and sympathetic predominance of ANS activity.

- The observed differences between persons with MP-related symptoms and persons with EHS indicated that the two conditions are distinct subgroups of EMF-related symptoms. It is likely that the heterogeneity within the group of persons with EMF-related symptoms will have consequences for the prognosis in the choice of remedial activities and medical treatment.
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