Petra Keski-Säntti

Occupational chronic solvent encephalopathy in Finland 1995–2007: incidence and diagnostic methods

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Address Finnish Institute of Occupational Health
Topeliuksenkatu 41 a A
FI-00250 Helsinki
Tel. +358- 30 4741
Fax +358-9 477 5071
www.ttl.fi

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ACADEMIC DISSERTATION

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Supervisor Docent Markku Sainio
Finnish Institute of Occupational Health
Department of Occupational Medicine,
Brain and Work Research Centre
Helsinki, Finland

Reviewers Professor Matti Hillbom
Department of Neurology, University of Oulu
Oulu, Finland

Docent Ville Jäntti
Department of Biomedical Engineering
Tampere University of Technology
Tampere, Finland
and
Department of Clinical Neurophysiology
Seinäjoki Central Hospital
Seinäjoki, Finland

Opponent Professor Juhani Juntunen
Etera Mutual Pension Insurance Company
Helsinki, Finland

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ABBREVIATIONS

BAEP	Brainstem auditory-evoked potentials
CANTAB	Cambridge neuropsychological test automated battery
CNS	Central nervous system
CSE	Chronic solvent encephalopathy
CT	Computerized tomography
CYP	Cytochrome P
DA	Dopamine
DEPS	Depression scale
DEY	Duration of exposure in years
DTI	Diffusion tensor imaging
DSM-IV	Diagnostic and statistical manual for mental disorders, fourth edition
EEG	Electroencephalography
ERP	Event-related potentials
FINJEM	Finnish job-exposure matrix
FIOH	Finnish Institute of Occupational Health
Fz	Electrode location on the frontal midline in electroencephalography
GABA	Gamma-aminobutyric acid
GST	Glutathione S-transferase
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAA	N-acetylaspartate
NMDA	N-methyl-D-aspartic acid
OEL	Occupational exposure limit
OELY	Occupational exposure limit years
OHS	Occupational health services

PET	Positron emission tomography
Pz	Electrode location on the parietal midline in electroencephalography
QEEG	Quantitative electroencephalography
SEP	Somatosensory evoked potential
SPECT	Single photon emission computed tomography
VEP	Visual evoked potential
WHO	World Health Organization
WCST	Wisconsin card sorting test

ABSTRACT

Background The occurrence of occupational chronic solvent encephalopathy (CSE) seems to decrease, but still every year reveals new cases. To prevent CSE and early retirement of solvent-exposed workers, actions should focus on early CSE detection and diagnosis. Identifying the work tasks and solvent exposure associated with high risk for CSE is crucial.

Methods Clinical and exposure data of all the 128 cases diagnosed with CSE as an occupational disease in Finland during 1995–2007 was collected from the patient records at the Finnish Institute of Occupational Health (FIOH) in Helsinki. The data on the number of exposed workers in Finland were gathered from the Finnish Job-exposure Matrix (FINJEM) and the number of employed from the national workforce survey. We analyzed the work tasks and solvent exposure of CSE patients and the findings in brain magnetic resonance imaging (MRI), quantitative electroencephalography (QEEG), and event-related potentials (ERP).

Results The annual number of new cases diminished from 18 to 3, and the incidence of CSE decreased from 8.6 to 1.2 / million employed per year. The highest incidence of CSE was in workers with their main exposure to aromatic hydrocarbons; during 1995–2006 the incidence decreased from 1.2 to 0.3 / 1 000 exposed workers per year. The work tasks with the highest incidence of CSE were floor layers and lacquerers, wooden surface finishers, and industrial, metal, or car painters. Among 71 CSE patients, brain MRI revealed atrophy or white matter hyperintensities or both in 38% of the cases. Atrophy – which was associated with duration of exposure – was most frequently located in the cerebellum and in the frontal or parietal brain areas. QEEG in a group

of 47 patients revealed increased power of the theta band in the frontal brain area. In a group of 86 patients, the P300 amplitude of auditory ERP was decreased, but at individual level, all the amplitude values were classified as normal. In 11 CSE patients and 13 age-matched controls, ERP elicited by a multimodal paradigm including an auditory, a visual detection, and a recognition memory task under single and dual-task conditions corroborated the decrease of auditory P300 amplitude in CSE patients in single-task condition. In dual-task conditions, the auditory P300 component was, more often in patients than in controls, unrecognizable.

Conclusions Due to the paucity and non-specificity of the findings, brain MRI serves mainly for differential diagnostics in CSE. QEEG and auditory P300 are insensitive at individual level and not useful in the clinical diagnostics of CSE. A multimodal ERP paradigm may, however, provide a more sensitive method to diagnose slight cognitive disturbances such as CSE.

TIIVISTELMÄ

Työperäisen liuotinaineaivosairauden esiintyvyys on viimeisten parinkymmenen vuoden aikana selvästi vähentynyt, mutta uusia tapauksia todetaan edelleen vuosittain. Liuotinaineaivosairauden ja sen seurauksena ennenaikaisen eläköitymisen ennaltaehkäisemiseksi on keskeistä tietää, missä työtehtävissä ja mille liuotinaineille altistuttaessa on olemassa riski sairastua liuotinaineaivosairauteen, jotta oireet voidaan tunnistaa ja aivosairaus diagnosoida mahdollisimman varhaisessa vaiheessa.

Väitöskirjassa on selvitetty liuotinaineaivosairauden ilmaantuvuutta vuosina 1995–2007 sekä missä työtehtävissä ja mille liuotinaineille altistuttaessa liuotinaineaivosairautta esiintyy. Lisäksi selvitettiin, minkälaisia muutoksia voidaan todeta aivojen magneettikuvauksessa (MRI), kvantitatiivisesti analysoidussa aivosähkökäyrätutkimuksessa (QEEG) sekä tapahtumasidonnaisissa jännitevastetutkimuksissa (event-related potentials, ERP).

Tutkimusaineistona oli kaikki 128 Työterveyslaitoksella vuosina 1995–2007 diagnosoidut liuotinaineaivosairaustapaukset. Kliiniset ja altistumistiedot kerättiin potilasasiakirjoista. Työllisten lukumäärä perustuu Tilastokeskuksen tilastoihin ja liuotinaineille työssään altistuvien työntekijöiden lukumäärä FINJEM-tietokantaan.

Tarkastelujakson 1995–2007 aikana vuosittain diagnosoitujen tapausten määrä väheni 18:sta 3:een ja ilmaantuvuus 8,6:sta 1,2 tapaukseen miljoonaa työllistä kohti. Ilmaantuvuus oli suurinta parketti- ja mattotöissä, huonekalujen ja puusepänteollisuustuotteiden maalaus- ja pintakäsittelytöissä sekä teollisuus-, metalli- ja automaalareiden keskuudessa. Altistumisen perusteella arvioituna suurin ilmaantuvuus oli työssään aromaattisille hiilivedyille altistuvien työntekijöiden keskuudessa.

Aivojen magneettikuvaus paljasti 38 %:ssa tutkituista tapauksista lievää aivoatrofiaa ja/tai poikkeavia muutoksia aivojen valkeassa aineessa. Atrofiaa, joka oli yhteydessä liuotinainealtistumisen kestoon, oli todettavissa erityisesti pikkuaivojen sekä otsa- ja päälakilohkon alueella. QEEG-tutkimuksessa theta-jakson absoluuttinen teho oli potilailla lisääntynyt otsalohkon alueella terveisiin verrokkeihin verrattuna. ERP tutkimuksessa kuuloärsykkeen aikaansaama P300-jännitevastekomponentin amplitudi oli potilailla pienentynyt ryhmätasolla verrattuna terveisiin verrokkeihin, mutta yksilötasolla amplitudit jäivät normaalivaihtelun rajoihin. Käytettäessä sekä kuulo- että näköärsykettä tehtävän aikana (dual-task paradigm) kuuloärsykkeen aikaansaama P300 vaste puuttui potilailta selvästi useammin kuin terveiltä verrokeilta.

Aivojen MRI-löydökset olivat lieviä ja epäspesifisiä, minkä vuoksi MRI-tutkimus soveltuu lähinnä liuotinaineaivosairauden erotusdiagnostiikkaan. Löydökset QEEG-tutkimuksessa olivat vähäisiä ja epäspesifisiä, eikä menetelmää voida suositella liuotinaineaivosairauden kliiniseen diagnostiikkaan. ERP-tutkimuksessa käytetyt paradigmat osoittautuivat epäherkiksi eivätkä ne sellaisenaan sovellu yksilötason diagnostiikkaan vaan vaativat edelleen kehitystyötä. Useamman paradigman yhdistämisestä syntyvä ERP-profiili tai monimuuttujamalli, jossa analysoidaan useita jännitevastekomponentteja, saattavat tulevaisuudessa tarjota herkemmän menetelmän lievien kognitiivisten häiriöiden, kuten liuotinaineaivosairauden, diagnostiikkaan.

1. INTRODUCTION

The history of occupational solvent neurotoxicity dates back to the 1850s, when the French physician Auguste Delpech reported severe neuropsychiatric symptoms in workers exposed to carbon disulfide in rubber manufacture (1,2). Carbon disulfide was one of the first industrial applications of a group of chemicals referred to as "organic solvents." In the 1900s, their industrial use expanded rapidly. The acute central nervous system (CNS) effects of these substances, e.g., unpleasant symptoms of dizziness, nausea, and fatigue, were recognized but regarded as reversible effects without permanent CNS damage (1).

Evidence for chronic CNS adverse effects related to occupational solvent exposure began to emerge in the early 1960s when the Finnish neuropsychologist Helena Hänninen published a case series of carbon disulfide intoxication in rubber manufacturing with chronic CNS effects at clearly lower exposure levels than in the cases of the 1800s (3). She proposed this "psycho-organic syndrome" or "organic solvent syndrome" as a new occupational disease.

Numerous epidemiological and cross-sectional studies have shown that long-term occupational exposure to various organic solvents may result in irreversible damage to the CNS (4). The existence of solvent-induced chronic toxic encephalopathy (i.e., organic brain disorder), also referred to as chronic solvent encephalopathy (CSE), was first acknowledged as an occupational disease in Finland, Sweden, Norway, and Denmark in the 1970s and in some European countries and the United States in the 1980s (2). In 1987, the National Institute for Occupational Safety and Health (NIOSH) in the United States recognized the neurotoxic potential of organic solvents for the human nervous system and gave recommendations to focus on occupational exposure

levels and hygienic actions (5). Worldwide, CSE is not, however, widely accepted as an occupational disease and even in European countries it is under-recognized, with national differences in the diagnostic procedure, litigation, and compensation (2,6,7). The present diagnostic criteria include substantial long-term exposure to organic neurotoxic solvents and typical symptoms together with signs of neurological and cognitive dysfunction described later on in this thesis.

Worldwide, millions of workers are occupationally exposed to organic solvents. In the United States alone, the estimated number of solvent-exposed workers is nearly 10 million, which is 3.7% of the general population (5,6). This corresponds to the estimate from New Zealand where around 100 000 workers, or 2.7% of the general population, were in the 1990s exposed to organic solvents (6,8). In Finland, in the 1990s about 50 000, but in the 21st century only 20 000 workers of the national workforce of 2.5 million (0.8% of the workforce and 0.4% of the general population) were occupationally exposed to organic solvents (9). The figures may be even ten-fold higher with occasional and very low-level exposure taken into account. During the last decades, the number of exposed workers and solvent exposure in many work tasks has diminished due to legislative, technical, and hygienic actions including substitution of less harmful water-based chemicals and introduction of closed processes (10–12). The prevention of solvent-related adverse effects has been possible in industrialized countries due to legislative actions and agreements between trade unions and employers (1,13). This has led to a decrease in the number of CSE patients, but still every year reveals new cases (14). Knowledge of the incidence and prevalence of CSE is, however, minimal.

CSE frequently leads to disability and early retirement (4,15–17). In order to maintain the work ability of solvent-exposed workers and to prevent CSE and early retirement, actions should focus on prevention of excess exposure, on recognition of symptoms related to solvent-related CNS adverse effects, and on early detection of CSE. Identifying the work tasks and solvent exposure associated with high risk for CSE is thus crucial. Diagnosis of CSE relies on evaluation of lifetime exposure, clinical examination, and comprehensive differential diagnostics by a multidisciplinary team. The non-specificity of symptoms, of clinical findings, and of results in diagnostic examinations renders the diagnostics of

CSE difficult. Furthermore, the verification of persistent, non-progressive cognitive dysfunction – the hallmark of CSE – by neuropsychological assessments is vulnerable to the interference of multiple confounding etiologies (18). It is thus important to evaluate the value of currently available diagnostic tools and to develop sensitive and valid diagnostic methods which may also elucidate the pathophysiological mechanism of CSE.

2. REVIEW OF THE LITERATURE

2.1 ORGANIC SOLVENTS

Worldwide, several hundred million tons of organic solvents have been widely used annually in household, industry, and other occupational settings. Millions of workers are regularly occupationally exposed to organic solvents considered neurotoxic (12).

2.1.1 Classification

Solvents are substances capable of dissolving or of extracting non-water-soluble substances (fats, oils, waxes, resins, rubber, asphalt, cellulose filaments, plastic materials) or of remaining in suspension without any chemical change in the material or the solvent (13). Compounds from many different chemical groups can serve as solvents (Table 1). The term "organic" refers to compounds that contain carbon bonds and in which at least one carbon atom is covalently linked to an atom of another type (commonly hydrogen, oxygen, or nitrogen). Organic solvents contain at least one carbon and one hydrogen molecule. Aliphatic compounds take the form of a chain, whereas aromatic compounds form a 6-carbon ring. For a hydrogen group may be substituted some other element such as a hydroxyl group in alcohols or a carbonyl group in ketones and esters. They may also contain a substituted halogen element (for example chloride) and are thus referred as halogenated hydrocarbons. Here, the term "solvent" refers to organic solvents.

Solvents are liquid compounds of low molecular weight, highly volatile in the ambient temperature. As a group, they share few physical features and even fewer chemical properties, but a common feature is lipophilicity and thereby affinity for the nervous system.

2.1.2 Occupational use

Solvents may be components in paints, varnishes, lacquers, adhesives, glues, and degreasing or cleaning agents, ones used, for example, in the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals (Table 1) (19). Workers in several occupations and work tasks, such as construction, industrial, metal, and car painting, printing-trade workers, floor layers and lacquerers, reinforced plastic laminators, and wooden surface finishers, are typically exposed.

Usually, solvents are used in mixtures to achieve optimal dissolving properties. A typical example is White spirit, also called mineral spirit, Stoddard solvent, mineral turpentine, petroleum spirit, or mineral naphtha, which is a mixture of aliphatic hydrocarbons with a content of aromatic hydrocarbons ranging from < 1 to 25%. It is widely used in cleaning and degreasing and in paints, lacquers, varnishes, and wood preservatives (19). Single-solvent exposure may occur, for example, in boat building and lamination (styrene), printing (toluene), and dry-cleaning (perchloroethylene).

2.1.3 Solvent abuse

Solvents have psychoactive effects causing an euphoric state, and thus solvent inhalation is a common form of substance abuse (20). The most commonly used inhalants are spray paints, paint thinners, and glues (products containing toluene and xylene), nail polish removers (acetone), and gasoline (21).

Because solvents are widely and easily accessible, legal, and inexpensive, a major problem among children and young adolescents worldwide, especially in lower economic groups and among minorities, is solvent abuse. It is typically initiated at the age of 8–14, at a younger age than, for example, abuse of alcohol or marijuana. Among Australian secondary school students, 6% of 12-year-olds but only 1% of 17-year-olds reported recent solvent abuse (22). Regular solvent abuse is much less common than experimental use: among American secondary school students, 1.2% of 13- to17-year-olds reported solvent abuse on 20 or more occasions, but even fewer meet criteria for drug dependence (23). In Finland, approximately 1–2% of adolescents have had experience with solvents (24).

Table 1. Occupationally used organic hydrocarbon solvents with neurotoxicity.

Chemical group	Compound (example)	Main occupational use and sources of exposure (example)
Aliphatic hydrocarbons	*n*-hexane	in glues, paints, lacquers, and printing inks; rubber and shoe industries
Aromatic hydrocarbons	Toluene	in paints, fuel oil, cleaning agents, lacquers, paint thinners; photogravure, printing, car and spray painting, linoleum laying
	Xylene	in paints, lacquers, adhesives, inks, varnishes, dyes, glues; polyester production, photogravure, spray painting, textile and rubber industry
	Styrene	in solvents, aircraft fuel; boat building reinforced plastic industry, fiber glass production synthesis and manufacture of polymers, copolymers, polyester resins.
	Benzene	in fuel, detergents, paint removers; rubber production, synthesis of a variety of chemical products. Use prohibited in 1982 except in closed systems and in research. If present in solvent mixtures, in concentrations of < 0.1 %
Chlorinated hydrocarbons	Trichloroethylene	in adhesives, paint removers; degreasing of metal components, dry cleaning, textile and leather industries
	Perchloroethylene	in metal degreasers; dry cleaning, textile industry
	Trichloroethane	in adhesives, inks, glues, paints; cold and dip cleaning, degreasing, metal work, printing, dry cleaning, leather work
	Methylene chloride	in metal degreasers, paint and varnish removers
	Carbon tetrachloride	in laboratory, dry cleaning, refrigerant use; in Finland restricted to analysis and research
Alcohols and glycols	Methanol, Ethanol, Propanol, Butanol,	in solvents and detergents
	Ethylene glycol	in antifreezes, a polymer precursor
Ketones	Methyl ethyl ketone	in adhesives, paints, dyes; cleaning, coating, paint stripping, in chemical and textile industries
Esters	Ethyl acetate	in paints, in laboratory work

Solvent abuse is especially harmful in late childhood and early adolescence, a crucial period for neuromaturation (25). Solvent abuse is associated with high rates of co-occurring behavioral and mental-health problems and serious medical, neurological, and neuropsychological impairments (20,21,25,26).

2.1.4 Pharmacokinetics

At an individual level, the uptake, distribution, biotransformation, and excretion of solvents modify their toxicity. In occupational settings, the main route of uptake is generally inhalation of solvent vapors. High solvent volatility and large surfaces of evaporation with significant concentrations of vapor in the air, lack of appropriate enclosure and exhaust ventilation systems, and relatively high temperature of the work environment all contribute to increased inhalation (27). As alveolar ventilation and pulmonary perfusion are functions of physical exertion, physical workload is related to increased solvent absorption. Uptake depends on the specific air-blood partition coefficients of each solvent which are determined by the alveolo-capillary membrane permeability and the solubility of the solvent in blood (28). Substances with low solubility, e.g., 1,1,1-trichloroethane, reach saturation levels at relatively low blood concentrations and cause less severe CNS disturbances, whereas styrene, with its high blood solubility and progressively rising blood concentrations, offers increased risk for CNS effects (27).

Part of the inhaled solvent is removed unchanged with expiration. The rest of the solvent is metabolized in the liver and removed as metabolites in the urine or to a lesser extent in the bile. Solvents and their metabolites are distributed to target tissues according to blood supply and lipid content of the organ system. Due to their low molecular weight and lipophilicity, solvents rapidly cross the blood-brain barrier and may accumulate in the brain, especially in myelin (29).

The toxicity and long-term effects of solvents depend on the toxicity of the solvent itself or its reactive intermediate metabolites. Metabolism of solvents occurs in the liver in two phases: Phase I – controlled by the cytochrome P450 (CYP) enzyme complex – yields reactive metabolites further detoxified in phase II (30). Many enzymes show genetic polymorphisms that may influence the neurotoxicity of solvents. The

phase I isozyme CYP2E1 is relevant to occupational toxicology because its substrate spectrum includes many solvents such as aliphatic, aromatic, and halogenated hydrocarbons. Evidence of the influence of CYP polymorphisms on the neurotoxicity of solvents is, however, limited (30–32). Instead, many enzymes of phase II, such as glutathione S-transferase M1 (GSTM1) and microsomal epoxide hydrolase (mEH), show genetic polymorphisms that affect the neurotoxicity of solvents. Individuals with the GSTM1 null genotype (GSTM1*0), for example, detoxify solvent metabolites more slowly than do those with the positive genotype (28,33–35). The relative proportion of the GSTM1*0 genotype is higher in CSE patients than in solvent-exposed non-CSE cases (33,36). The same predominance of the GSTM1*0 genotype is evident in solvent-exposed workers with psychiatric, neurologic, or cognitive symptoms (especially deficits in sustained attention and short-term memory) compared to asymptomatic workers (34). Heavily solvent-exposed individuals with the GSTM1*0 genotype also appear to be at increased risk for Parkinson's disease (37). GSTM1 thus seems to play a protective role against the neurotoxic effects of solvents.

Solvents mainly serve as mixtures, which renders the estimation of their pharmacokinetics difficult. Interactions between solvents are complicated, and their biological synergistic effects have been incompletely characterized. Solvents may inhibit or induce each other's metabolism, and their effects on each other may be additive, synergistic, or potentiated (28). Enzyme competition and induction may occur also between solvents and alcohol or drugs. Alcohol, for example, elevates the formation of styrene-7,8-oxide, a highly toxic metabolite of styrene (29). Blood levels of toluene and xylene increase acutely with concomitant alcohol ingestion, whereas workers chronically ingesting alcohol have lower blood levels of toluene and xylene due to metabolizing enzyme induction (38,39).

2.2 NEUROTOXICITY OF SOLVENTS

A chemical is considered neurotoxic if it is capable of inducing a consistent pattern of structural (i.e. neuroanatomical) change or neural dysfunction that causes neurochemical, neurophysiological, or behavioral effects (40).

2.2.1 Neuroanatomical changes

Myelin, with a lipid content of about 70%, is particularly vulnerable to the effects of lipophilic substances and is thus one of the suggested target structures of solvent neurotoxicity. In subjects abusing toluene, a known myelinotoxic solvent, neuropathological examinations have revealed brain atrophy and gliosis as well as thinning of the corpus callosum and damage to myelin with axonal sparing (20,26). Brain magnetic resonance imaging (MRI) has revealed diffuse brain atrophy, callosal thinning, and loss of gray matter – white matter boundaries, hyperintensities in the white matter, and hypointensity in the thalami and basal ganglia in T_2 -weighted images, findings indicating demyelination (26,41–45). In magnetic resonance spectroscopy (MRS), lowered N-acetylaspartate (NAA), elevated myo-inositol, and unchanged choline levels in the centrum semiovale and cerebellum indicate, however, that the principal neuropathological mechanism in chronic toluene encephalopathy is axonopathy and gliosis, not active demyelination (46). The volume of cortical gray matter has in MRI also been reduced in frontotemporal and parietal areas (47). MRS has, in the thalamus – a neuron-rich gray matter structure – shown normal NAA, suggesting, however, absence of direct neuronal damage (46).

Alcohol abuse and the effects of ethanol on CNS are widely studied and may serve as a model to understand the pathophysiological mechanisms of other solvents, as well. Neuropathological examination of alcoholics reveals reduced brain volume which is mainly attributable to a reduction in white matter (48–49, 51–52), MRI of alcoholics has shown thinning of the corpus callosum, reduced volume of both white and gray matter, and white matter hyperintensities in T_2 -weighted images (50). Even in cases where the macrostructure of the white matter appears normal in MRI, magnetic resonance diffusion tensor imaging (DTI), which permits quantification of the directionality and coherence of white matter fiber tracts, shows lowered fractional anisotropy (a measure reflecting the magnitude and orientation of white matter tracts) in the centrum semiovale and the genu of the corpus callosum (50,56). The MRI findings may, however, be reversible and attributable not only to the neurotoxic effects of alcohol, but also to, for example, vitamin deficiency, electrolyte disturbances, or nutritional and hormonal factors (48,51,56).

The only autopsy study on CSE patients revealed no neuropathological abnormalities (57), and animal studies have also failed to reveal gross histopathological changes related to chronic solvent exposure (58,59). Studies on nerve-specific marker proteins (e.g., neuron-specific enolase, creatine kinase-B, beta-S100, glial fibrillary acidic protein) in rats exposed to toluene or white spirit indicate, however, activation of astrocytes and gliosis in the white matter (59–61). In CSE patients, no abnormalities have emerged in the nerve-specific marker proteins in cerebrospinal fluid (62). Elevated protein concentrations in the cerebrospinal fluid of CSE patients suggest, however, a protein leak through the damaged blood brain barrier (63) and a slight lymphoid reaction indicates non-specific immunoactivation (64,65).

Brain MRI findings of solvent-exposed workers and CSE patients have been normal or have revealed central or cortical atrophy (66–73). Some of the MRI studies have also revealed changes similar to those seen in association with toluene and alcohol abuse, i.e. reduced corpus callosum volume, loss of gray-white matter discrimination, periventricular white matter hyperintensities, and hypointensity in the basal ganglia in T_2 -weighted images, suggesting solvent effects on white matter (70,72,74). MRS have on the one hand shown increased choline levels in the thalamus, basal ganglia, and parietal white matter in solvent-exposed workers, indicating demyelination (72). On the other hand, a reduced choline, NAA, and N-acetylaspartyl-glutamate level in the frontal gray matter in CSE patients indicates abnormalities in neuronal viability and axonal density (72). The only DTI study on CSE patients failed to reveal abnormalities in the white matter tracts (73). All the MRI findings are, however, non-specific. Even cases with chronic toxic encephalopathy due to acute massive solvent intoxication present with non-specific MRI findings (75,76).

Structural neuroanatomical changes in the CNS related to solvent exposure and also to non-occupational exposure, seem to include neuronal loss, axonopathy, and demyelination, although the pathophysiological mechanism is unconfirmed.

2.2.2 Neurochemical changes

Cell cultures and animal studies indicate that solvents induce changes in the lipid structure of cell membranes which interfere with synaptic

membrane transport mechanisms and disturb intercellular communication (29,77). They also interact with the lipophilic portions of cell proteins which disrupt, for example, fast axonal transport of proteins such as neurofilaments (29). The neurotoxic mechanisms may differ from one solvent to another, but a common factor is the ability to promote the synthesis of reactive oxygen species (78,79). This may lead to free-radical-induced lipid peroxidation, mitochondrial and nucleic acid damage, and oxidative stress, all of which play a role in the early phases of neuronal apoptosis (78,80,81).

The effects of solvents involve complex interactions with neurotransmitters and ion channel systems. The effects of ethanol on neurotransmitters have been widely studied in relation to alcohol abuse (82). Ethanol-induced inhibition of the release of glutamate – an excitatory neurotransmitter in the CNS – and potentiation of the activity of gamma-aminobutyric acid (GABA) – a major inhibitory neurotransmitter – contribute to the acute depressive effects of ethanol on the CNS (83,84). Ethanol, as well as some other solvents such as toluene, benzene, xylene, and 1,1,1-trichloroethane, acutely inhibits the function of one of the glutamate receptors, the N-methyl-D-aspartic acid (NMDA) receptor (84,85). Chronic exposure causes adaptive up-regulation in the sensitivity of NMDA receptors, which results in an increased vulnerability to glutamate-induced excitotoxicity (77,85,86). NMDA receptors also mediate influx of Ca^{2+} ions to the cell, which results, for example, in production of reactive oxygen species, release of stored glutamate, and increased excitotoxicity (77,85).

Animal studies have revealed chronic solvent effects on monoamine (dopamine (DA), serotonin, and noradrenaline) and cholinergic neurotransmitter systems (87). The best evidence of solvent effects on neurotransmitters exists for the dopaminergic system (Fig. 1). The high vulnerability of the DA system to toxic effects results from the functional and morphologic properties of DA neurons. The axons of DA neurons are slow-conducting, small-diameter fibers with a low conduction safety factor and a large projection area (88). The fact that DA neurons in the hypothalamus and ventral tegmental area are in direct contact with the walls of capillary vessels means greater risk for exposure to exogenous substances present in blood (88).

Styrene has been shown to induce in solvent-exposed workers an increase in prolactin secretion from the anterior lobe of the pituitary gland, suggesting selective vulnerability of DA neurons in the hypothalamus, because prolactin secretion is directly controlled by the activity of the tuberoinfundibular pathway (TIDA) which runs from the hypothalamus to the pituitary gland (Fig. 1) (89–91).

That solvents enter the body mainly through the respiratory system makes the olfactory mucosa and olfactory receptors particularly vulnerable to their toxic effects. Dopamine-synthesizing periglomerular cells in the olfactory bulb are functionally related to the DA system. DA neurons from the ventral tegmental area project into limbic forebrain structures (nucleus accumbens, olfactory tubercle, amygdala) and cortical areas (medial prefrontal cortex, entorhinal cortex) to form the mesocorticolimbic DA projection system (Fig. 1) (88). Damage to the rhinencephalic (limbic and medial-temporal) structures causes disturbances not only in olfaction, but also in cognitive functions such as learning and memory.

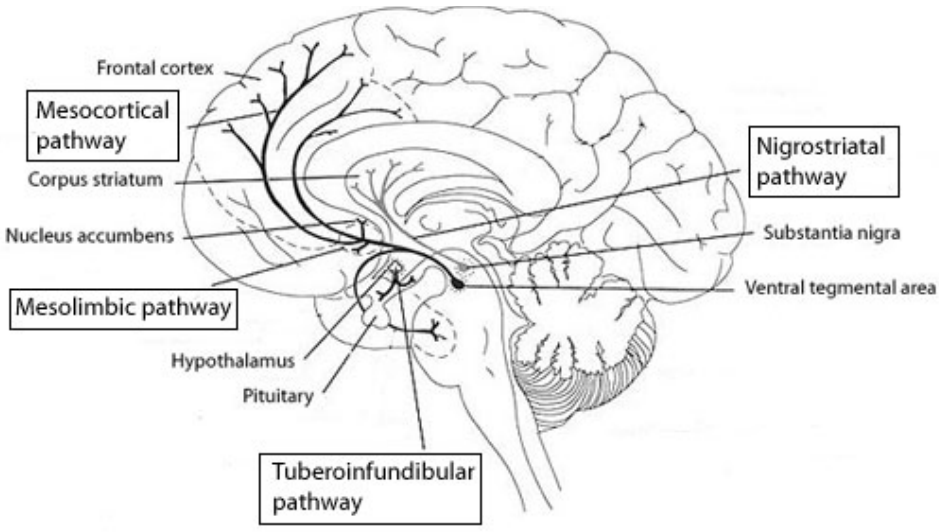


Fig. 1. Sagittal section of the brain showing the main dopaminergic pathways. Adapted with permission from *Australian Prescriber* (Fig. 3 in Crocker AD. Experimental and clinical pharmacology: Dopamine – mechanisms of action. Aust Prescr 1994;17:17–21.)

The DA system is also involved in most visual sensory and perceptual functions (88). Lowered visual contrast sensitivity and impaired color vision discrimination found in solvent-exposed workers and CSE patients (92–97) may be partly due to an interference of solvents with the dopaminergic mechanism of retinal cells, although toxic demyelination of optic nerve or disturbances at higher cortical levels may also be involved (94,98,99).

Solvent exposure also affects the nigrostriatal DA projection system. Long-term exposure to organic solvents has been shown to increase the rate of dopamine synthesis in the brain without affecting the number of presynaptic terminals or postsynaptic dopamine receptors (100). This may result from solvent-enhanced catalytic activity of the dopadecarboxylase enzyme or as a response to reduced dopamine D_2-receptor affinity (101). A recent study has shown reduced striatal D_2 binding in CSE patients and also in asymptomatic solvent-exposed workers, indicating more specific postsynaptic damage (73).

Exposure to some solvents, such as carbon disulfide, *n*-hexane, methyl alcohol, toluene, methanol, trichloroethylene, and several solvent mixtures, has been associated with parkinsonism (88,102–107). Moreover, two case-control studies have shown that patients with Parkinson's disease (PD) have been exposed to solvents more frequently than have healthy referents (108,109). Occupational exposure to hydrocarbon solvents is also a risk factor for earlier onset of PD symptoms and a more severe disease course (110,111). Case reports involving positron emission tomography (PET) for patients with signs of parkinsonism and long-term occupational exposure to hydrocarbons have revealed similar but more severe and widespread DA dysfunction and loss of dopaminergic nerve terminals than in PD, and also a reduction in dopamine D_2 binding sites in the caudate nucleus not present in idiopathic PD (102,104).

2.2.3 Neurophysiological changes

Electrophysiological methods provide information on electrical neuronal activity. Evoked potentials are electrical responses of the brain generated by a sensory (visual, auditory, or somatosensory) stimulus and provide information regarding sensory tracts from the site of stimulation to the brain cortex. Abnormalities in evoked potentials indicate disturbances

in white matter. Results in visual evoked potential (VEP), somatosensory evoked potential (SEP), and brainstem auditory evoked potential (BAEP) studies on solvent-exposed workers and CSE patients have been inconsistent; they have been normal or have shown prolonged latency and both decreased and increased amplitudes (98,112–121).

In electroencephalography (EEG), synchronous electrical activity produced by the firing of large neuronal populations in the brain is recorded with electrodes attached to the scalp. EEG has excellent time resolution, but tissues between the source and the electrodes attenuate and distort the EEG signal. EEG may reflect both local and global cerebral dysfunction with limited exact source localization ability.

EEG is divided into frequency bands reflecting different degrees of brain activity; delta (1–3 Hz), theta (3.5–7.5 Hz), alpha (8.0–11.5 Hz), beta (12–28 Hz), and gamma (28.5–50.0 Hz). In a healthy, awake subject, beta rhythm predominates over anterior, and alpha rhythm over posterior brain areas (122). Cortical disorders are related to loss of faster frequencies, whereas subcortical disturbances such as vascular dementia cause non-specific focal or diffuse slow-wave abnormalities, i.e., increased theta or delta activity (122). Aging is associated with slowing of EEG, decreased amplitude of alpha activity, and increased theta and delta power (123). In chronic alcoholism, the most frequent finding is an increase in beta power, but increased theta activity, especially in central and parietal areas, has also been reported (124,125). EEG studies on solvent-exposed workers and CSE patients have revealed either normal activity or increased beta activity and mainly diffuse but in some cases focal slow wave abnormalities (15,115,126–131). In addition, quantitatively analyzed EEG (QEEG) has revealed increased total power and differences in the anteroposterior distribution, i.e., increased power over anterior and decreased power over posterior areas (69,115,116,130,132–134).

EEG reflects spontaneous electrical activity in the brain, whereas event-related potentials (ERP), the so-called "cognitive potentials," provide information on electrical responses related to cognitive processing. ERPs are generated in tasks where subjects attend to and discriminate between stimuli that differ from one another in some dimension. A classical paradigm is the "oddball" paradigm in which an infrequent target occurs in a background of frequent standard stimuli, and the subject is required to respond to the infrequent target stimuli (Fig. 2) (135).

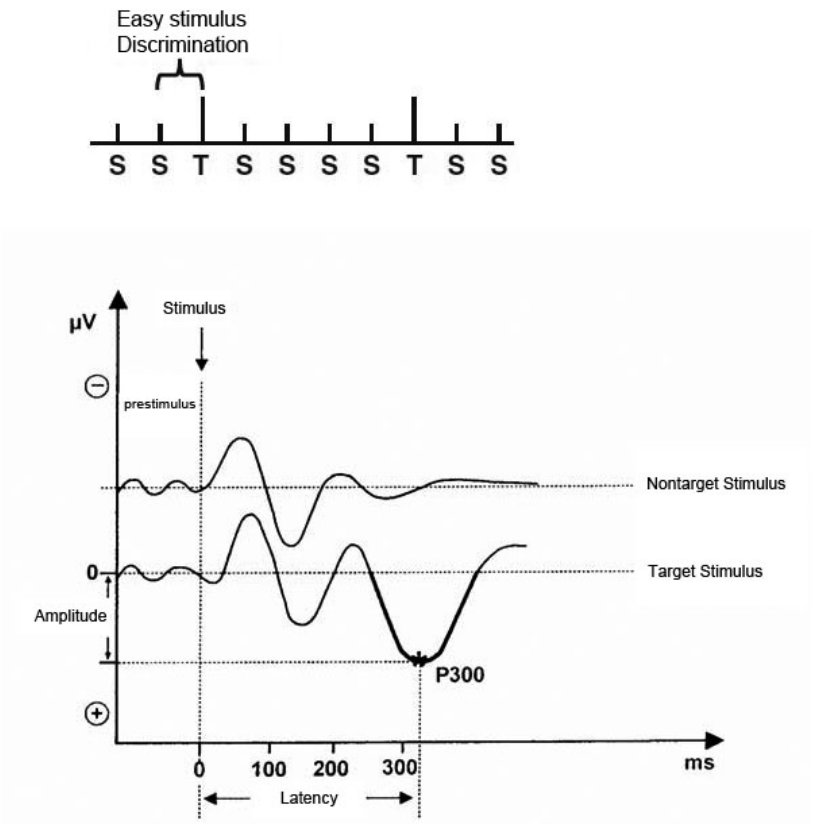


Fig. 2. Schematic illustration of the oddball paradigm with standard (S) and target (T) stimuli presented in a random sequence and the elicited ERP with P300 response from the target but not from the non-target (standard) stimuli. Reprinted with permission from S. Karger AG, Basel, Copyright © (1999) from Frodl-Bauch T et al., Neurochemical substrates and neuroanatomical generators of the event-related P300, Neuropsychobiology 1999;40(2), page 87.

The late components of ERP, such as P300 (a positive waveform with peak latency at about 300 ms after the stimulus), represent attention allocation, activation of immediate memory, memory updating, and decision-making (137). Changes in P300 latency and amplitude occur in many conditions affecting cognitive processing, such as in depression,

PD, and Alzheimer's disease (138–140). P300 amplitude decreases and latency is prolonged also in aging (141). Reduced P300 amplitude is associated with several factors, such as drugs, medication, and smoking (135,142). In alcoholics, P300 amplitude is decreased, and the decrease persists also after long-term abstinence (143). The effects of alcohol abuse on ERP may be related to the neurotoxic effects of alcohol. As ERPs are, however, genetically determined, the reduced P300 amplitude may also reflect genetic predisposition to alcoholism; the P300 amplitude is reduced also in the non-alcoholic relatives of alcoholics (143,144).

In solvent-exposed workers and CSE patients, findings in auditory P300 studies have been inconsistent; they have been normal (120) or shown either prolonged P300 latency (145,146) or decreased amplitude (134). Visual ERP studies have revealed decreased P300 amplitude and prolonged latency (114,147).

2.2.4 Solvent effects on cognitive functions

The most consistent cognitive deficits in occupationally solvent-exposed workers and CSE patients are related to attention, performance speed, and memory, especially working memory function (148–153). Similar, although more severe, disturbances and even dementia may occur in association with toluene abuse (26,44,45).

Working memory refers to short-term storage, manipulation, and organization of information; it relies on ability to control attention (154). Attention can be described as the sustained focus of cognitive resources on one aspect of the environment while ignoring or filtering out other things. Competitive selection is the process that determines which information gains access to working memory. Top-down attention control refers to goal-directed selection of stimuli and response, whereas bottom-up saliency filters automatically enhance the response to infrequent and unexpected stimuli (Fig. 3) (155).

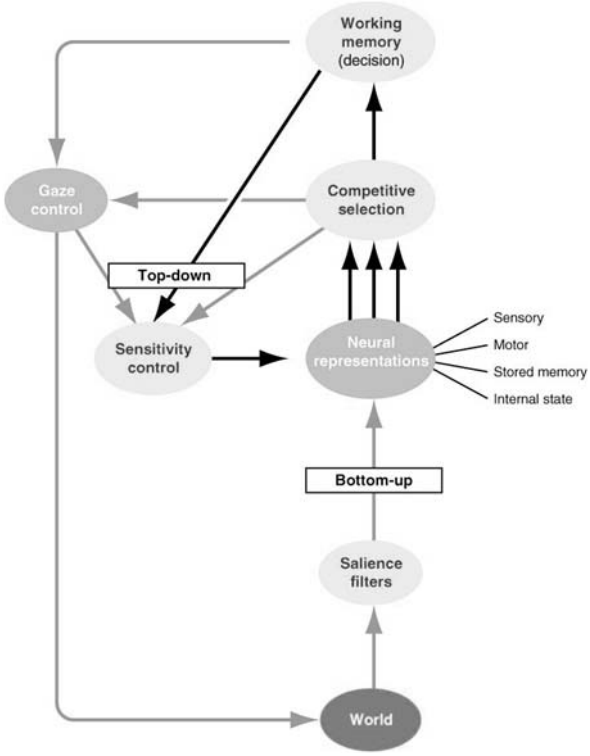


Fig. 3. Functional components of attention. Information about the world is processed by salience filters that respond differentially to infrequent or important stimuli (bottom-up). A competitive process selects the representation for entry into the circuitry that underlies working memory. Working memory can direct top-down bias signals that modulate the sensitivity of representations that are being processed in working memory. The selection process can also direct top-down bias signals that reflect the result of the competitive selection. Working memory and competitive selection direct eye movements and other orienting behaviors. Voluntary attention involves working memory, top-down sensitivity control, and competitive selection operating as a recurrent loop (dark arrows) (155). Reprinted from Annual Review of Neuroscience 2007(30), page 59, with permission from Annual Reviews, Copyright © 2007.

Functional neuroimaging has shown that tasks requiring working memory activate the prefrontal, parietal, and anterior cingulated cortex as well as parts of the basal ganglia (Fig. 4) (156,157). Striatal dopaminergic function mediates working memory capacity and, for example, load-dependent prefrontal cortex activation, which also leads to changes in the activity of parietal regions (158–160). Dorsolateral prefrontal cortex is involved in organization, manipulation, and encoding of information and is activated together with the dorsal parietal cortex in top-down attention control (Fig. 4) (161,162). Dorsolateral prefrontal cortex is suggested to act as a trigger for the dorsal parietal cortex to, for example, disengage and shift attention to a previously unattended stimulus. Selecting, comparing, and deciding on information held in memory activates the ventrolateral prefrontal cortex, which is involved together with the ventral parietal cortex in bottom-up attention control (Fig. 4) (162,163). The dorsal part of the anterior cingulate cortex, which is connected to the prefrontal and parietal cortex, motor brain areas, and frontal eye fields, is a central station for processing top-down and bottom-up stimuli and is involved in attentional processes to initiate action and suppress inappropriate responses (163).

In solvent-exposed workers with cognitive impairment, PET during a working memory task has revealed activation of the frontal cortex in atypical areas, suggesting neural compensation (164). Functional compensation in frontal areas has also been evident in aging, which is, as is CSE, accompanied by slowed information processing speed and a decline in working memory and attentional abilities (157,165,166).

The neuropsychological deficits in CSE resemble qualitatively those of Parkinson's disease (148,167). In Parkinson's disease, they have been linked to nigrostriatal dopamine depletion which disrupts the normal pattern of basal ganglia outflow and affects normal transmission of information through the frontostriatothalamic circuitry (168,169). This circuitry, which connects the frontal lobes to the basal ganglia and mediates cognitive, behavioral, and motor functions, accounts for psychomotor speed (168). Impaired psychomotor speed has in CSE patients and asymptomatic solvent-exposed workers been shown to associate with reduced striatal D_2 binding (73), a reduction associated also with impairment in neuropsychological tests requiring abstraction and mental flexibility, attention, and response inhibition, i.e., frontal brain functions; it has been shown to be associated also with aging (170,171).

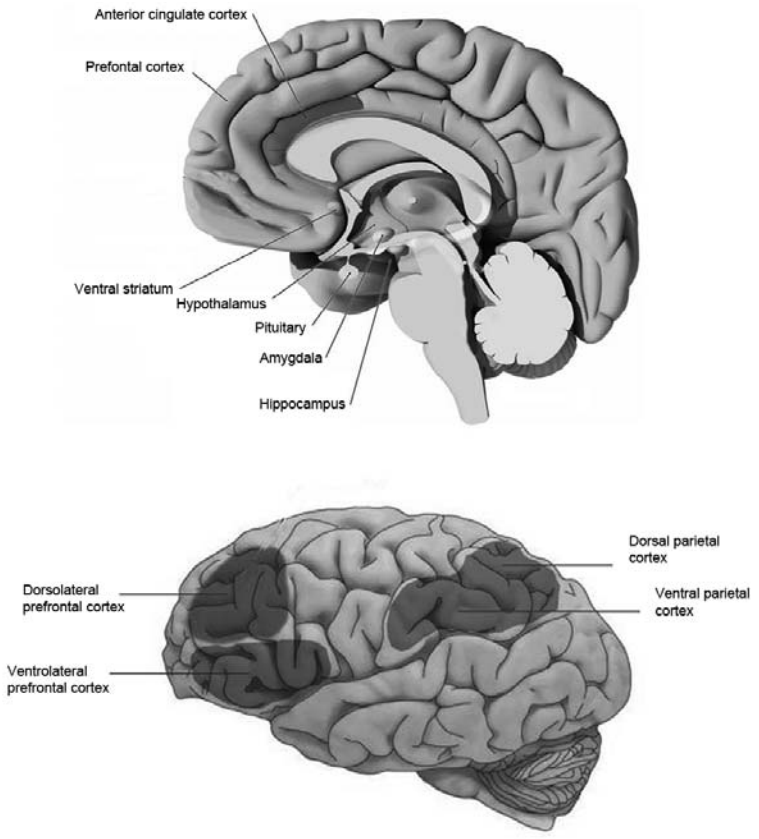


Fig. 4. Brain areas involved in working memory and attention. Copied under license from the Canadian Medical Association and Access Copyright © 2009, from aan het Rot et al., Neurobiological mechanisms in major depressive disorder, Canadian Medical Association Journal 2009;180(3);page 310. Further reproduction prohibited.

In alcoholics, their cognitive deficits (deficits in abstract problem-solving, visuo-spatial and verbal learning, perceptual motor skills, speed of information processing, attention, and working memory) may also be related to disruption of DA connectivity within the prefrontal region and between frontal and parietal regions. A reduced number of cholinergic neurons in the basal forebrain and changes in cholinergic neurotransmission, however, also account for the cognitive disturbances seen in alcoholism (56,86,172–174).

Cognitive deficits related to CSE seem to share similarities with alcoholism, Parkinson's disease, and aging, and suggest fronto-temporo-parietal dysfunction related to disturbances in frontostriatothalamic circuitry. The cognitive performance of CSE patients corresponds to that of 20-year-older healthy subjects (175,176). It has thus been hypothesized that in CSE the neurotoxic solvent effects lead to premature aging (58,175), a hypothesis suggested also in association with alcoholism (177).

2.3 OCCUPATIONAL CHRONIC SOLVENT ENCEPHALOPATHY

Acute solvent exposure typically causes symptoms such as dizziness, disorientation, euphoria, and a feeling of drunkenness – symptoms somewhat resembling those seen with excessive alcohol use. Increasing levels of solvent exposure may lead to confusion progressing to unconsciousness, convulsions, and death. The acute, transient effects of solvents result from their pharmacological actions and subsequent neurochemical changes in the CNS, which does not necessarily indicate neurotoxicity (40). Acute massive exposure (178) and long-lasting low-level solvent exposure (15,179) has, however, proven neurotoxic and may lead to non-reversible chronic encephalopathy.

2.3.1 Epidemiology

Worldwide, knowledge as to the prevalence and incidence of CSE is limited. In New Zealand, with a population of about 4.2 million, 76 CSE cases were diagnosed between 1993 and 1997 (3.6 cases per million inhabitants annually) (8). A more recent survey from the Netherlands, with a population of 16 million, reported 396 CSE cases between 1997 and 2006 (2.5 cases per million inhabitants annually) (180). In 1997, a European survey estimated the incidence of CSE which varied from 0.1 to 16.8 cases per million employed (2). This huge variety in incidence is partly due to national differences in the diagnostic procedure, criteria, and acceptance of CSE as an occupational disease. Studies on the incidence of CSE in populations at risk, i.e., those occupationally exposed to organic solvents, are lacking.

2.3.2 Diagnostic criteria

In 1985, a working group of the World Health Organization (WHO) presented diagnostic criteria and a classification for solvent-induced chronic toxic encephalopathy (Table 2) (181). Two years later, the "Workshop on neurobehavioral effects of solvents" in Raleigh, North Carolina, USA, introduced a somewhat different classification which divides patients of WHO class II into those with sustained personality or mood change (type 2A) and those also with impairment of cognitive functions (type 2B) (182).

Table 2. Classification of chronic solvent encephalopathy according to WHO

	Symptoms	Cognitive deficits	Neurological deficits
Class I Organic affective syndrome	Fatigue, difficulties in memory and concentration, loss of initiative. Change in personality, poor impulse control, lowered mood and motivation, irritability, anxiety, emotional lability	No objective dysfunction	No
Class II Mild chronic toxic encephalopathy	Difficulties in concentration and attention, impairment of memory, decrease in learning capacity	Objective evidence of cognitive impairment	Minor neurological signs
Class III Severe chronic toxic encephalopathy	Marked global deterioration in intellect and memory	Marked global deterioration in intellect and memory	Neurological signs or neuroradiological findings

The International Classification of Diseases, tenth edition (ICD-10), classifies CSE as a toxic encephalopathy (G92) with a defined causal agent (*T52.x; organic *solvents) (183). The Diagnostic and Statistical Manual for Mental Disorders*, fourth edition (DSM-IV), lacks any specific code for CSE, but it can be classified as a substance-induced persistent dementia (292.82), amnestic (292.83), or other cognitive disorder (294.9) (184).

Worldwide, the diagnostic criteria and classification of CSE are used inconsistently. In 1998, only 8 of 18 centers in European countries, the United States, and New Zealand used the WHO or Raleigh classification. The other centers used ICD-10, DSM-IV, or some national classification (6).

The diagnosis of CSE relies on (1) verification of substantial long-term exposure to organic neurotoxic solvents, (2) a characteristic clinical picture of organic nervous system damage with typical subjective symptoms and objective findings in clinical and auxiliary examinations, (3) exclusion of other organic brain disorders and primary psychiatric diseases (7,181,182,185). In 1994, an expert group convened by the European Commission suggested requesting a minimum duration of exposure of 10 years (186). Less may be accepted in cases with particularly high concentrations. Later, the latency between cessation of exposure and symptoms has been restricted to no more than a few months (187).

2.3.3 Diagnostic procedure

The initial step in CSE diagnostics is the recognition of symptoms as solvent-related adverse effects. Euroquest – a neurotoxic symptom questionnaire – has proven feasible in the early recognition of neurotoxic symptoms, for example, in primarily health care or occupational health services (OHS) (188,189). In Finland, cases with a suspicion of CNS adverse effects related to occupational solvent-exposure are, after primary differential diagnostics (exclusion of depression, sleep disturbances, and alcohol abuse as the primary cause), referred to the Finnish Institute of Occupational Health (FIOH) in Helsinki, where the diagnostic procedure has been centralized since the 1990s (185).

The diagnostic procedure at the FIOH includes evaluation of all previous medical records and available documents relating to exposure, interviews and clinical examinations by specialists in occupational medicine and neurology, brain imaging with MRI, differential diagnostic laboratory testing, and at least one, usually several, comprehensive clinical neuropsychological assessments. If other possible causes of cognitive dysfunction – most often psychiatric or sleep disorders – are suspected, further studies are carried out. Other examinations, such as EEG, evoked potentials, ERP, ophthalmic and visual function examinations,

and analyses of cerebrospinal fluid have been useful, but their diagnostic value has remained undetermined. The diagnosis of CSE is made after a follow-up of at least one year to exclude reversible or progressive symptomatology. During follow-up, occupational solvent exposure is halted or is minimized, and other possible medical disorders are treated. Finally, clinical and neuropsychological re-evaluations are carried out, and the CSE diagnosis is verified by a multidisciplinary team (14,185).

The survey of van der Hoek et al (6) revealed that in 1998 in most of the European countries, the United States, and New Zealand, an occupational physician and a neuropsychologist usually examine the patients, and neurologists, psychiatrists, and occupational hygienists are consulted when necessary. Blood tests, EEG, brain imaging, electroneuromyography, and evoked or event-related potentials were used on indication only (6). The expert group convened by the European Commission stated in 2009 that the diagnosis should be established as a result of examinations by a specialist in occupational medicine, a neurologist, and a neuropsychologist in conjunction (187).

2.3.4 Assessment of exposure

Assessment of occupational solvent exposure is essential in the diagnostics of CSE but is difficult to qualify and quantify. Worldwide, assessment of exposure in clinical settings is variable. Some centers use interviews, measurements at the workplace, biological monitoring, industrial hygienic data and job-exposure matrix, or exposure indices calculated in several ways (6).

Classification of lifetime exposure solely by duration of occupational solvent exposure in years may result in misclassification of subjects, because the level of solvent exposure, content of solvent mixtures, and working conditions change over time (190). Retrospective assessment of life-time solvent exposure based on recall is also prone to errors and over- or underestimation of exposure (191,192). Biological markers, for example urinary hippuric acid levels for toluene and mandelic acid levels for styrene, can serve in the assessment of exposure to single solvents. Current biological monitoring and hygienic measurements at the workplace are useful for surveillance of exposed workers but are unsuitable for assessment of past exposure. The most valid assessment procedures

are job-specific questionnaires and detailed interviews combined with an evaluation by an expert (192,193).

Exposure indices, which can be calculated in several ways, provide an estimate of cumulative dose and intensity of lifetime exposure (194,195). Occupational Exposure Limit Years (OELY) has been used at FIOH. One OELY is equivalent to working eight hours a day for one year with solvent exposure at the level of the Finnish Occupational Exposure Limit (OEL) of 1981, which correspond to the concurrent threshold limit values of the American Conference of Governmental Industrial Hygienists (196). In clinical practice at FIOH, six or more OELY is considered requisite for the diagnosis of CSE, assuming that all the other diagnostic criteria are met (14).

2.3.5 Symptoms and clinical signs

CSE patients present with a wide variety of non-specific neurological, mood-related, and cognitive symptoms. The most prevalent symptoms include headache, dizziness and imbalance, sleeping problems, fatigue, irritability, emotional lability, decreased initiative, and depressed mood (see Table 2). The hallmark of CSE is the cognitive symptoms: impaired memory and difficulties in concentration (14,16,189,197,198). This symptom domain in Euroquest also has the best power in discriminating between workers with CSE and unexposed referents (188,189). The symptoms of CSE are non-progressive and are usually alleviated slightly after cessation of exposure, although difficulties in memory and concentration tend to remain (189,199).

The clinical neurological examination is usually normal or may reveal slight non-specific abnormalities such as disequilibrium, impaired fine motor control, and dyscoordination (15,126,197,198).

2.3.6 Diagnostic methods

Brain imaging

Brain computerized tomography (CT) of CSE patients may be normal or reveal slight brain atrophy (66,197,200,201). MRI, which is more sensitive in assessing brain atrophy and white matter changes (66), may

also be normal or reveal central and cortical atrophy (66,70,73). One MRI study on CSE patients has also revealed loss of gray-white matter discrimination, periventricular white matter hyperintensities, and hypointensity in the basal ganglia in T_2 -weighted images, indicating solvent effects in the white matter (70).

Single photon emission computed tomography (SPECT), which measures blood flow in the brain and indirectly brain metabolism, has in CSE patients revealed decreased blood flow mainly in temporal, frontal, and parietal areas (127,202,203). PET with fluorodeoxyglucose, a direct measure of glucose metabolism, has in two CSE case reports, one with long-term solvent exposure and one with acute tetrabromoethane intoxication, revealed fronto-parietal and subcortical (basal ganglia, amygdala, hippocampus) hypometabolism (204,205).

Neurophysiological methods

EEG in CSE patients may be normal or reveal increased beta activity and mainly diffuse but in some cases local slow wave abnormalities (increased theta and delta power) (15,126–128,131). Due to large individual variation in EEG and subjective visual interpretation of the recordings, this method is less sensitive in revealing slight brain involvement. QEEG provides a more sensitive and objective method to analyze electrical activity of the brain. In CSE patients it has revealed increased beta or total power and differences in the anteroposterior distribution of electrical activity (132,134).

Decreased amplitude may be visible in VEP (114),(98,112–118) and auditory or visual ERP may reveal prolonged latency or decreased amplitude of the P300 component (114,134,145,146). The only ERP study with a dual task paradigm has also shown decreased ERP amplitudes (134).

Neuropsychological assessment

In the clinical neuropsychological assessment, CSE patients show mild to moderate deficits in memory and learning, attention and allocation of attentional resources, visuospatial functions, abstract reasoning, and speed of information processing (148,149,151–153)

In order to standardize clinical assessments and diagnosing of CSE, the WHO advised in 1986 a standardized core battery of neuropsychological tests focusing on psychomotor functioning, memory, and attention (181). The survey of van der Hoek et al revealed, however, that in 1998 in most of the European countries, the United States, and New Zealand, the neuropsychological test batteries used in clinical practice were heterogeneous (6). The expert group convened by the European Commission suggested in 2009 that the neuropsychological test battery should include tests of verbal and visual memory, attention, psychomotor speed, and abstraction ability. Primary intellectual ability, previous intellectual level, and education should be evaluated, as well as cooperation and effort during the tests (187).

Auxiliary methods

Ophthalmic and visual function examinations of CSE patients may reveal lowered visual contrast sensitivity and impaired color vision discrimination (92–94). Audiological and otoneurological tests may reveal hearing loss and disturbances in the vestibulocerebellar system (206–209). Hyposmia may also be discovered (210). Laboratory tests are usually normal and serve mainly as differential diagnostic tools (211). Cerebrospinal fluid examination is also usually normal, but may reveal non-specific abnormalities such as a slight lymphoid reaction or an increase in protein concentration (62–64).

Case report

A 48-year-old man, who had been working as a spraypainter and a sandblaster for 28 years, was diagnosed with CSE in 1995. He had no other diseases and used no medication. He had been smoking for 33 years, and his reported alcohol consumption was on average 4 to 5 doses per week. He had been exposed mainly to White spirit, xylene, and butanol, and the exposure had been heavy (OELY 16). This solvent-exposure work halted in 1994.

The clinical neurological examination was normal. The neuropsychological assessment revealed impaired psychomotor speed, slight dyspraxia,

difficulties in allocation of attention, impairment of verbal memory, and interference with memory functions.

The brain MRI in 1994 revealed slight non-specific changes in deep white matter (Fig. 5). In the CSF analysis, the proportion (72%) of cells in the monocyte-macrophage line was increased, indicating chronic CNS irritation. EEG and ERP were recorded in 1994 and in 1995. The visual EEG readings were normal. The quantitative analysis of the EEG in 1994 revealed increased delta activity throughout the brain, especially over the frontocentral area, and a slight increase emerged over the convexity in the theta activity. The P300 latency of auditory ERP was prolonged in both of the recordings (380.7 ms and 385.5 ms), and in the second recording, the P300 amplitude was decreased (5.8 μV and 4.4 μV) (Fig. 5). VEP in 1995 was normal. Ophthalmic and visual function examinations revealed slight congenital protanopia; otherwise no abnormalities appeared in color vision, contrast sensitivity, or visual fields. It was stated that the patient was unable to any work, and he was granted a disability pension. During the follow-up of six years, the patient's condition, symptoms, and findings in neurological and neuropsychological examinations remained stable. He was also diagnosed with occupational asthma and occupational perceptive hypoacusis.

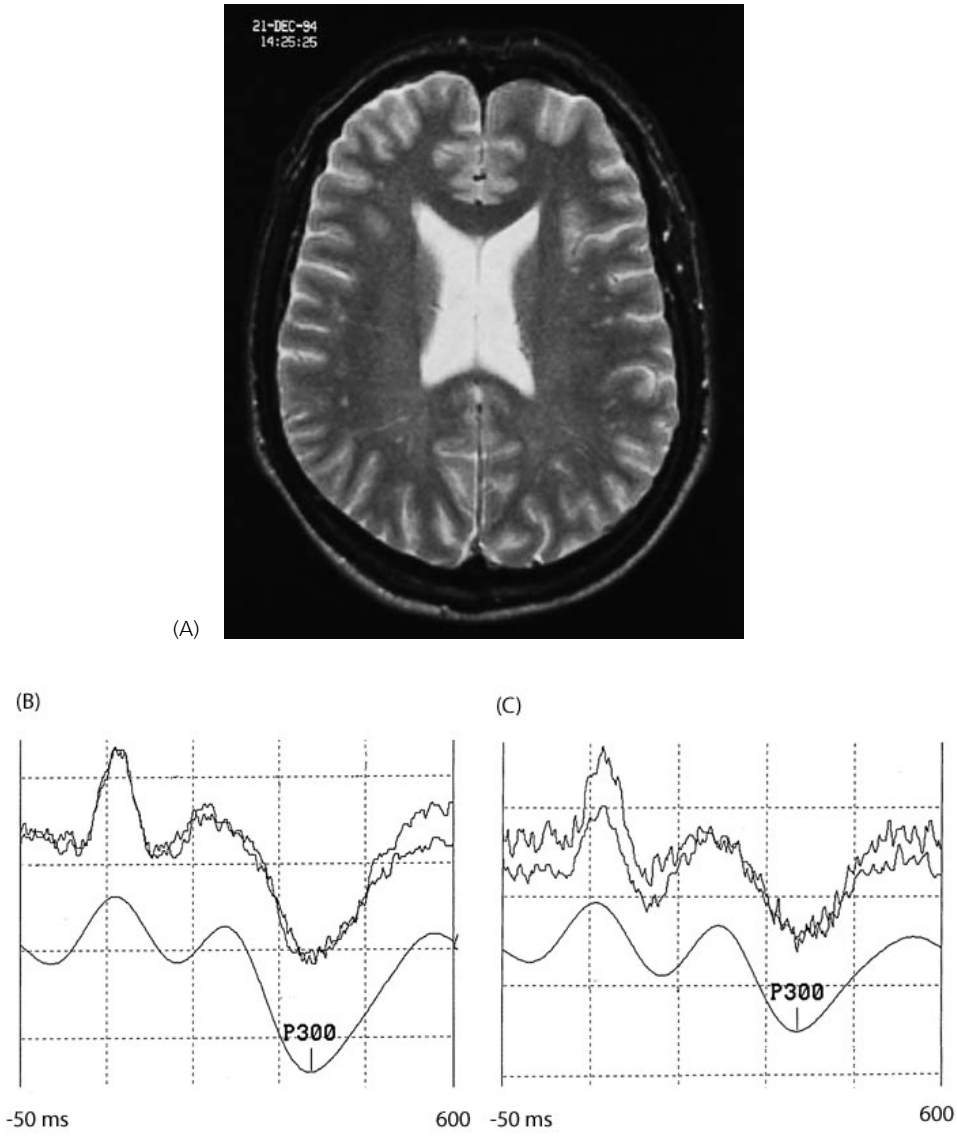


Fig. 5. (A) The brain MRI of a 48-year-old spraypainter-sandblaster diagnosed with CSE in 1994 revealed small focal hyperintensities in deep white matter in T_2 -weighted images. (B) The auditory ERP in 1994 revealed prolonged P300 latency (380.7 ms) but normal amplitude (5.8 μV). (C) In 1995, the P300 latency was prolonged (385.5 ms) and amplitude decreased (4.4 μV). The lower response curve is filtered with 6 Hz lowpass.

2.3.7 Differential diagnoses

In the differential diagnostics of CSE, CNS disorders such as cerebrovascular diseases, neurodegenerative disorders (Alzheimer's disease, Parkinson's disease), infections and inflammatory brain diseases (multiple sclerosis), neoplasms and paraneoplastic syndromes, and traumatic brain disorders must be excluded. Other conditions which share similarities with the symptoms and cognitive dysfunction in CSE include metabolic causes (avitaminosis, thyroid disorders), depression, sleep disorders, and alcohol- or substance abuse (187).

Major depression shares many symptoms with CSE such as fatigue, loss of initiative, memory impairment, difficulty in concentration, and irritability (184) and is thereby a differential diagnostic challenge. The most typical axis I mood disorders in CSE patients and solvent-exposed workers are depression and anxiety (212,213). It is, however, difficult to determine whether the psychiatric symptoms in CSE have an organic etiology or are psychological reactions secondary to a decrease in functionality and quality of life (214,215).

Psychiatric and mood symptoms may also contribute to poor performance in neuropsychological tests (216). Many other potentially confounding and effect-modifying factors, such as pre-exposure intellectual capacity, developmental learning difficulties, education, alertness in the test situation, pain, alcohol use, and medication, influence neurobehavioral test performance and make the interpretation difficult (18,217). Furthermore, patients with suspected CSE may be involved in litigation or financial compensation procedures depending on the national compensation system and may show insufficient effort and suboptimal performance in test situations (153,218).

CSE patients frequently report sleeping problems, such as diminished sleep quality, difficulties falling asleep, frequent awakenings and trouble falling asleep again, waking up too early, and feeling tired upon awakening (189). These symptoms may be related to, for example, mood disorders but also to solvent exposure itself (219). Symptoms of sleep apnea syndrome, such as fatigue, forgetfulness, and concentration problems, are also very similar to those reported by CSE patients, and it has been argued that solvent-exposed workers with sleep apnea could have been

misdiagnosed as CSE cases (219,220). Solvent exposure may, however, induce or at least aggravate sleep apnea (219–222).

Chronic alcohol abuse frequently associates with disturbances in working memory, learning, visuospatial abilities, executive functions, and psychomotor speed (174,223) which may be difficult to distinguish from the ones caused by long-term occupational solvent exposure. Excessive alcohol consumption and risk for alcoholism is increased among solvent-exposed workers and thus must be considered in differential diagnostics (224–226). Ataxia and polyneuropathy often associated with alcohol abuse are, however, typically absent in CSE (15,185,197,227).

Other concurrent etiologies do not, however, prohibit the diagnosis of CSE as an occupational disease. In Finland, the diagnosis can be made if occupational etiology is considered to account for at least 50% of the etiology.

3. AIMS OF THE STUDY

The aims were distributed among the five studies as follows:

Study I defined the number and incidence of CSE cases in Finland during 1995–2007, evaluated the duration and nature of exposure, identified the work tasks where CSE was encountered, and elucidated the consequences of CSE for the patient's work ability and reasons for rejection of CSE diagnosis in suspected cases.

Study II characterized the brain MRI findings in CSE patients and evaluated the diagnostic value of brain MRI in CSE.

Study III characterized the QEEG findings in CSE patients and evaluated the diagnostic value of QEEG in CSE.

Study IV characterized the P300 component of auditory ERP in CSE. It also evaluated the implication of the results for the diagnostics of CSE and for the understanding of the pathophysiology of CSE.

Study V aimed to develop a more sensitive ERP method for the diagnostics of CSE and to improve the understanding of the brain dysfunction and pathophysiology of CSE.

4. MATERIALS AND METHODS

4.1 Patients and controls

The diagnosis of occupational CSE of all the patients included in the five studies had been done according to the routine clinical diagnostic procedure at FIOH. All patients fulfilled the criteria for non-reversible and non-progressive toxic encephalopathy due to occupational solvent exposure type 2B according to the classification by the International Solvent Workshop or class II of the WHO criteria (181,182). Brain MRI (Study II), EEG (Study III), and ERP (Study IV) had been part of the clinical diagnostic procedure. Clinical and exposure information was collected from the patient records of FIOH.

Study I: incidence, solvent exposure, and work tasks of CSE patients

The material consisted of all patient records of CSE cases diagnosed at FIOH during 1995–2007. Records of the patients referred during 2002–2004 were analyzed in detail to reveal CSE patients' ability to work. We also included all the workers referred to FIOH during 1995–2005 due to a suspicion of CSE to study the proportion of those diagnosed among all referred cases. Of the cases referred during 2002–2004, we also analyzed the main reasons for rejection of a CSE diagnosis.

Study II: magnetic resonance imaging of the brain

In order to characterize the brain MRI findings in CSE, clinical information on 153 patients diagnosed at FIOH between 1991 and 2003 with occupational chronic toxic encephalopathy was collected from patient

records. Exclusion criteria were toxic encephalopathy due to other than solvent exposure, such as lead or aluminium encephalopathy, brain imaging only with CT, any other concomitant brain disorder, previous traumatic brain injury, and alcohol consumption exceeding on average 1200 g absolute alcohol per month (40 g or 3–4 units of absolute alcohol per day) for men and 820 g for women during the preceding year. Two patients with encephalopathy due to acute solvent intoxication were excluded. MRI data on 25 patients was unavailable for re-analysis of the images. The final number was 71. Patient characteristics are in Table 4.

Study III: quantitative electroencephalography

During 1994–2000, an EEG recording had been done for 59 CSE patients without any other brain disorder, previous traumatic brain injury, or psychiatric disease apart from depression. Exclusion criteria for reported alcohol consumption were applied as in Study II. Because of gender differences in EEG, females (n=7) were excluded from the study, as were four patients on benzodiazepine and one on carbamazepine medication. The final number of patients was 47. Eight of them were on a medication with an influence on the central nervous system (CNS medication), such as tricyclic antidepressants or selective serotonin reuptake inhibitors.

We used two control groups. The male blue-collar workers of the age-matched control group had participated during 1991–1995 in a large study at FIOH investigating the predictors of work capacity and disability pension in aging construction workers (228). In that study, 200 subjects had been randomly selected from the original sample of 1000 subjects for further medical, neurophysiological, and neuropsychological evaluation. From this data set, we excluded 77 subjects (39%) due to a job-title indicating possible occupational solvent exposure. A further 23 subjects were excluded by the same exclusion criteria as for CSE patients. The final number of age-matched controls was 100. For the laboratory's reference EEG values, healthy subjects had been recruited mainly from the staff of FIOH, and the 24 male subjects formed the laboratory control group. Characteristics of patients and the controls are in Table 4.

Study IV: auditory event-related potentials

Auditory ERP recording had been done for 104 (83%) of the 125 patients diagnosed with CSE at FIOH during 1993–2002. Patients excluded due to some other brain disorder, previous traumatic brain injury, psychiatric disease apart from depression, or excessive alcohol consumption (criteria applied as in Study II) numbered 34. We also excluded two patients with encephalopathy due to acute solvent intoxication and three patients with unidentifiable ERP waves. The final number of patients was 86, with eight female. Ten patients were on CNS medication: antidepressants, anxiolytics, or analgesic drugs. A second ERP recording, done an average 14 months (range, 10–18) after the first one, involved 19 patients.

We used two control groups. The age- and education-matched control group was selected from the same worker population as in Study III by the same exclusion criteria. As the ERP waves of two control subjects were unidentifiable, the final number of matched controls was 108 with eight being female. None of the matched controls was on CNS medication. The laboratory's own reference ERP values on the 84 healthy subjects, recruited mainly from the staff of FIOH, formed the laboratory control group.

In order to compare ERP results to cognitive parameters, we chose three subtests from the Wechsler Adult Intelligence Scale (WAIS) or WAIS-revised that measure various aspects of attention and short-term memory functioning: Digits Forward, Digits Backward, and Digit Symbol Substitution (229,230). These tests had been part of the comprehensive clinical neuropsychological assessment during the clinical diagnostic procedure of all CSE patients in the auditory ERP study. The same tests were also part of the neuropsychological test battery of the matched controls (228).

CSE patients' performance was inferior to that of the matched controls on all three neuropsychological tests (Table 3). Characteristics of patients and controls are in Table 4.

Table 3. Performance of patients with chronic solvent encephalopathy and age- and education-matched controls in neuropsychological tests

	Patients (n=86)			Controls (n=108)			
	mean	SD	range	mean	SD	range	*p*-value
Digits Forward	5.4	1.0	3–8	6.0	1.1	3–9	<0.001
Digits Backward	4.0	1.0	2–7	4.5	1.2	2–8	<0.001
Digit Symbol Substitution	30.3	8.8	16–60	35.5	10.2	13–67	<0.001

Study V: multimodal event-related potentials

All 16 patients diagnosed with CSE at FIOH during 2004–2007 were asked to participate in the study. In order to perform a follow-up study on the cognitive performance of CSE patients, 10 patients diagnosed during 2001–2003 – ones who had participated in a study (unpublished) at FIOH in 2004–2005 characterizing the memory performance profile of CSE patients – were also contacted. Refusals and non-reachable cases numbered 11. One case was excluded from the study group due to technical failure in ERP registration and three cases due to depression. The final number of patients was 11, one female. The mean time from the CSE diagnosis to the study was 3.7 years (SD 2.0, range 1–8).

The age-matched control group comprised 13 subjects without any history of solvent exposure or neurological diseases. All the patients and controls completed a questionnaire inquiring about their education, health, medication, and alcohol consumption. None of the patients or controls had previous traumatic brain injury, depression or any other psychiatric disease, or excessive alcohol consumption (criteria applied as in Study II).

Characteristics of patients and the controls are in Table 4.

Table 4. Characteristics of chronic solvent encephalopathy patients and their controls in Studies II–V.

	Study II[a]	Study III[b]			Study IV[c]			Study V[d]	
	Patients n=71	Patients n=47	Controls n=100	Laboratory-controls n=24	Patients n=86	Controls n=108	Laboratory-controls n=84	Patients n=11	Controls n=13
Age (years)									
Mean (SD)	51.0 (7.2)	50.6 (5.8)	50.1 (6.8)	39.8 (9.0)	50.1 (6.3)	49.8 (6.8)	41.1 (10.2)	59.5 (3.8)	59.4 (4.5)
range	33–73	33–61	40–65	25–65	34–61	40–65	20–63	53–66	52–66
DEY[e]									
Mean (SD)	27.1 (8.1)	27.5 (8.1)	0	0	27 (7.5)	0	0	33.5 (8.1)	
range	11–49	11–43			11–43			17–42	
OELY[f]									
Mean (SD)	10.8 (4.4)	10.7 (4.2)	0	0	10.8 (4.4)	0	0	11.0 (3.8)	
range	6–23	5–21			6–26			7–17	
Alcohol consumption (g/month)[g]									
Mean (SD)	173 (226)	205 (259)	381 (341)	NA	158 (199)	364 (338)	NA	140 (154)	137 (162)
range	0–960	0–1080	0–1154	NA	0–768	0–1154		0–480	0–480
Smokers (%)	37	30	NA	NA	34	43	NA	27	0
Hypertension (%)	13	13	NA	NA	17	13	NA	27	15
Diabetes (%)	6	6	NA	NA	6	0	NA	0	0
Education (years)									
Mean (SD)	NA	NA	NA	NA	7.2 (1.4)	7.1 (1.9)	NA	9.1 (1.2)	12.2 (3.5)
range					6–12	4–15		7–11	6–19

[a] Magnetic resonance imaging study without controls
[b] Electroencephalography study
[c] Auditory event-related potentials study
[d] Multimodal event-related potentials study
[e] Duration of occupational exposure in years
[f] Occupational exposure limit, years
[g] Alcohol consumption during the preceding year was asked in a questionnaire, patients in Studies II, III, and IV had also been interviewed during the diagnostic procedure. Alcohol consumption during the days preceding examinations was not asked.
NA=not available

4.2 Assessment of depression

In the auditory ERP study (Study IV), a specialist in psychiatry re-evaluated the psychiatric records of the 72 CSE patients (84% of the 86 patients in the study group) who had during the diagnostic procedure at FIOH undergone a psychiatric assessment. Patients who at the time of ERP recording had fulfilled the diagnostic criteria of current major depressive episode according to DSM-IV (184) numbered 21. Patients who had reported depressive symptoms not fulfilling DSM-IV criteria were 11, and those without depressive symptoms were 40. In the multimodal ERP study, the current mood of the patients and controls was screened by the Depression Scale (DEPS) (231).

4.3 Cognitive parameters

In the multimodal ERP study, the patients and controls performed computerized cognitive tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition Ltd, UK), measuring working memory performance, efficiency of learning, and various aspects of attention. The test battery included Spatial Span (SSP), Intra-Extra Dimensional Set Shift (IED), Rapid Visual Information Processing (RVP), Spatial Working Memory (SWM), and Paired Associate Learning (PAL) (232–234). Verbal task instructions were standardized, and all assessments were done by the same trained investigator. After the ERP recording, all subjects performed the tasks in the same order via a 15-inch touch-screen in a quiet, semi-darkened room. Due to technical failure, two controls missed taking the cognitive tests and thus the final number of controls was 11.

4.4 Assessment of exposure

In Study I, which characterizes the work tasks and solvent exposure of CSE patients, an industrial hygienist analyzed the lifetime solvent exposure of each patient, identified and classified the main solvents in the exposure, and categorized the main exposure-work according to a

list of 20 common work tasks with solvent exposure. Data were based on the detailed work and exposure description in the patient records.

In all five studies, we used two indices of long-term solvent exposure. The Duration of occupational solvent Exposure in Years (DEY) is the actual time at exposure-work excluding periods without solvent exposure, e.g., during unemployment or disability leave. OELY takes into account also the intensity of lifetime exposure. Estimation of OELY is based on a work description including ventilation and use of personal protective devices, duration of exposure work, and characterization of solvents and exposure levels. If measurements at workplaces were unavailable, we used hygienic data from similar workplaces, gathered over the years in the FIOH's Register of Industrial Hygiene Measurements. One OELY is equivalent to working eight hours a day for one year with the solvent exposure at the Finnish Occupational Exposure Limit (OEL). The equation OELY = $\sum i C_i t_i$, where C_i is the average solvent exposure level in ith work task expressed as a percentage of the Finnish OEL of 1981, and t_i is the total duration in years of the work in the ith task. For example, a patient had been working as a painter for 37 years, during 1955–1991. He had been doing active painting for 3 hours per day, 11 months per year. His exposure had been mainly to toluene, xylene, alcohols, ketones, ethyl acetate, and gasoline. During 1955–1986, the use of solvent-based paints had been 10 to 20 liters per day, but during 1987–1991 only one liter per day. During 1955–1984 (30 years) the exposure was at the level of OEL, and the solvent exposure level was 3 ÷ 8 x 1.0 OEL = 0.375 OEL. Measurements at his workplace revealed that during 1985–86 (2 years) solvent exposure level was 40% of the OEL. The solvent exposure level was thus 3 ÷ 8 x 0.4 OEL = 0.15 OEL. During 1987–1991 (5 years) the proportion of solvent-based paints of all paints was only 10%. The solvent exposure level was 0.10 x 3 ÷ 8 x 0.4 OEL = 0.02 OEL. The equation of OELY is 11 ÷ 12 (30 years x 0.375 OEL + 2 years x 0.15 OEL + 5 years x 0.02 OEL) = 10.7 OELY.

In the EEG study (III), we also used the ratio of OELY and DEY as a measure of relative intensity of exposure.

4.5 Assessment of incidence

The Finnish Job-Exposure Matrix (FINJEM) provides information on the number of exposed workers in Finland by occupation, agent, and level of exposure (235). To estimate the incidence of CSE in the solvent-exposed workforce, we compared the number of CSE cases to the number of (1) solvent-exposed workers and (2) workers exposed at high solvent exposure-levels (> 50% of the occupational exposure limit, OEL) during 1960–2006. The FINJEM data was classified according to agent, i.e., solvents classified into four groups: (1) aliphatic and alicyclic hydrocarbons, (2) aromatic hydrocarbons, (3) chlorinated hydrocarbons, and (4) other organic solvents (alcohols, ketones, esters, ethers, carbon disulfide, and glycol compounds). The total number of those employed in Finland, in different provinces, and in different work tasks came from the national workforce survey (236).

4.6 Magnetic resonance imaging

MRI of the CSE patients had been performed with a 1.0 or 1.5 Tesla scanner (Siemens Magnetom, Erlangen, Germany) between 1991 and 2001 as a part of their diagnostic procedure. Transaxial T_2- (T_R 2200ms, T_E 80 ms) and PD- (T_R 2200 ms, T_E 13 ms) or T_2- (T_R 4000 ms, T_E 99 ms) and FLAIR- (T_R 9999 ms, T_E 105 ms, T_I 2500), as well as coronal T_2- or T_1-weighted (T_R 600 ms, T_E 15 ms) images, had been produced. The slice thickness had been 5 mm for transaxial and 4 mm for coronal sections and the number of slices 19–20 on every pulse sequence.

In Study II, the MRI scans were independently re-evaluated by two experienced neuroradiologists, blinded to the original MRI assessment, exposure data, and results of other examinations. Periventricular (capping and lining) and deep white matter hyperintensities were analyzed according to a validated rating system: small (<5 mm) and large (6–10 mm) focal lesions and focal (11–26 mm) and diffuse (>26 mm) confluent lesions (237). White matter hyperintensities in the corpus callosum, cerebellum, and brain stem, as well as hypointensities in basal ganglia and thalamus were recorded. No more than five small (<5 mm) focal deep white matter hyperintensities, small periventricular caps, and thin lining

were regarded as normal. Brain atrophy in 13 brain areas (cortical and central atrophy in frontal, parietal, temporal, and occipital brain areas, and in the cerebellum as well as atrophy in the vermis, brainstem, and corpus callosum) was rated visually in comparison to standard images which show a series of brain scans of successively increasing ventricular size and widening sulci from normal (grade 1) to severe brain atrophy (grade 8) (238). Ventricular size and sulcal width of more than grade 4 were considered abnormal. An atrophy sum-score reflecting the extent of atrophy was calculated for each CSE patient by giving one point for atrophy in every single brain area. The MRI finding was considered positive if both the neuroradiologists agreed. If they disagreed, the lower rating was chosen.

4.7 Electroencephalography

EEG had been recorded between 1994 and 2000 as a part of the patients' diagnostic procedure. The subjects were sitting, eyes closed, in an armchair in a quiet and dim room, but had been instructed to stay awake. Electrodes were attached to the scalp according to the international 10–20 system (Fig. 6).

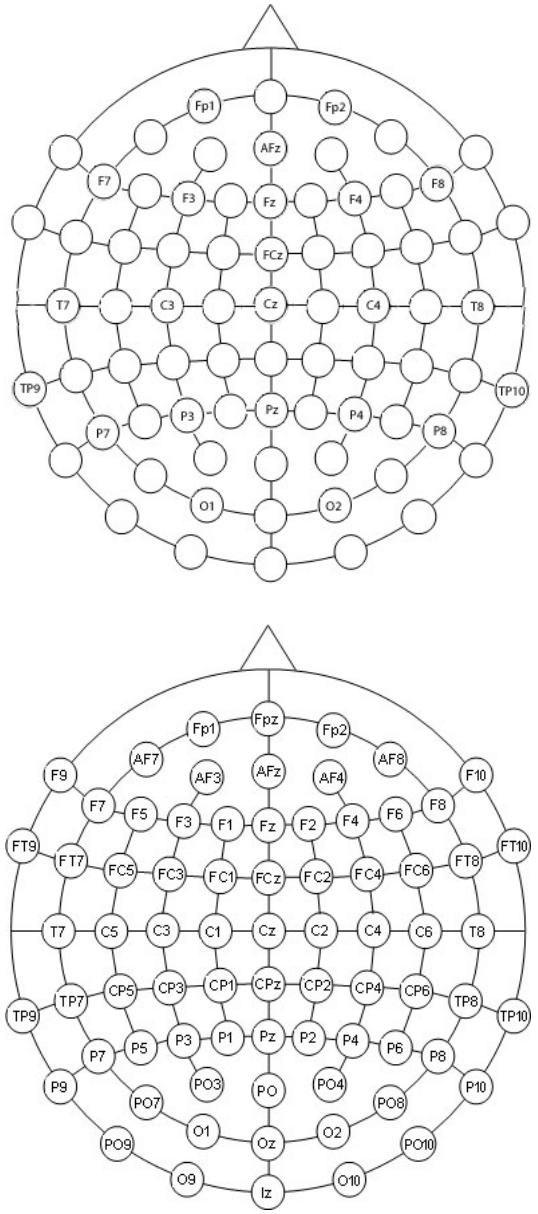


Fig. 6. Location and nomenclature of EEG electrodes according to the international (A) 10–20 system and (B) 10–10 system. F = frontal, Fp = frontal polar, T = temporal, C = central, P = parietal, O = occipital. Electrodes are numbered odd on the left side of the brain and even on the right side of the brain. Electrodes on the center (midline) are appended with the letter z.

Two additional electrodes were an Fpz electrode (between the Fp1 and Fp2 electrodes) and an Oz electrode (between the O1 and O2 electrodes). Recording was performed with Cadwell Spectrum 32 equipment with 21 channels. The signal was filtered with a 70-Hz low-pass filter and a 50-Hz notch filter. The visual interpretation, choice of epochs, and quantitative analyses were performed off-line with a Cadwell RDC-32 reading station with the Neurometrics program. For the quantitative analysis, 24 epochs lasting 2.5 seconds each (60 sec total) were gathered. The frequency band analyzed was divided into the delta (1.5–3.5 Hz), theta (3.5–7.5 Hz), alpha (7.5–12.5 Hz), and beta band (12.5–25.0 Hz). In monopolar montages (A1A2 as reference), absolute power values had been analyzed in these bands in all 21 channels. The total power values were summed from the power values of delta, theta, alpha, and beta bands. The number of variables had been reduced by calculating regional means from the original variables: the frontal region (Fp1, Fp2, Fpz, F3, F4, and Fz), temporal (T3, T4, T5, and T6), centroparietal (C3, C4, Cz, P3, P4, and Pz), and occipital region (O1, O2, and Oz). Finally, a clinical neurophysiologist provided his clinical statement based on the statistical analyses of these 20 EEG variables. EEG was performed in the same way with the laboratory and age-matched controls. In Study III, the data of these 20 EEG variables from all the patients and controls were collected and analyzed.

4.8 Auditory event-related potentials

The auditory ERP recording in Study IV had been performed on the patients between 1994 and 2002 as one part of their clinical diagnostic procedure. A Cadwell Spectrum 32 system was used to perform the oddball paradigm. Tones were presented with a varying interstimulus interval (1.72–1.96 s) binaurally at a 70 dB sound pressure level (a 10 ms rise time, 30 ms plateau time, and 10 ms fall time). The frequency was 1000 Hz for standard tones and 2000 Hz for target tones. Two 256-trial blocks were presented, each containing 64 (25%) target stimuli in random order. Two consecutive 256 trial blocks had been carried out to control repeatability of the recording.

All subjects had been examined sitting in a chair while awake with eyes closed. The research technician observed the alertness and perform-

ance of the subject; in cases with artefacts, recording was momentarily interrupted. Before recording, an example of the task was presented to ascertain that all the subjects could easily discriminate the target from the standard tones. The subjects were asked to count silently the number of target stimuli.

The event-related potential (bandpass 0.5–80 Hz) was recorded at the Pz electrode site (International 10–20 system, see Fig 5). Linked ears (A1A2) served as a reference. Waveforms were averaged on-line by the Cadwell Spectrum 32 system, which also controlled the quality of the response and rejected artefacts: Trials in which EEG exceeded ± 80 μV were automatically rejected on-line. The analysis time was 650 ms including a 50 ms pre-stimulus baseline. The mean responses were digitally filtered (6 Hz lowpass), and responses from both trial blocks were compared visually to ensure repeatability. Only waveforms present in both stimulus blocks were considered adequate responses for the analyses. The amplitude of P300 was measured relative to the 50 ms pre-stimulus baseline and the latency from the onset of the stimuli. The auditory ERP had been performed in the same way for the laboratory and age-matched controls. In Study IV, data on the ERP variables from all the patients and controls were collected and analyzed.

4.9 Multimodal event-related potentials

In the multimodal ERP study (Study V), we used three tasks: (1) an auditory "oddball" (AUD) (see Fig. 2), (2) a visual detection (VIS), and (3) a recognition memory (MEM) task. AUD consisted of 515 auditory stimuli (presented for 50 ms with a rise and fall time of 10 ms, 60 dB over auditory threshold) presented through headphones (Telephonics TDH-39P). The frequent standards (1000 Hz, 80% probability) and the infrequent deviants (1500 Hz, 20% probability) were presented randomly so that at least two frequent standards appeared between the infrequent targets. The sequence was the same for each trial. The inter-tone interval was 700 ms. The subjects were instructed to push the button with their left hands as fast as possible when hearing the targets.

MEM was a modified matching-to-sample version of the Sternberg paradigm (239). Three black letters randomly selected from the English

alphabet were presented on a light gray background on a 19-inch computer monitor for 2300 ms, followed immediately by a single target letter presented for 2000 ms. The subjects were instructed to push the button with their right hand as fast as possible only when the target had been included in the previous set (Fig. 7). The inclusion probability in the 90 trials was 50%, and the target was equally often at the first, second, and third position of the three-letter set.

VIS was identical with the memory task in structure and presentation times. Instead of three letters, three symbols "XXX" were presented on the monitor. The target symbol was either an "O" (inclusion, probability 50%) or an "X" (exclusion). The subjects were instructed to push the button with their right hand as fast as possible only when seeing the target "O" (Fig. 7).

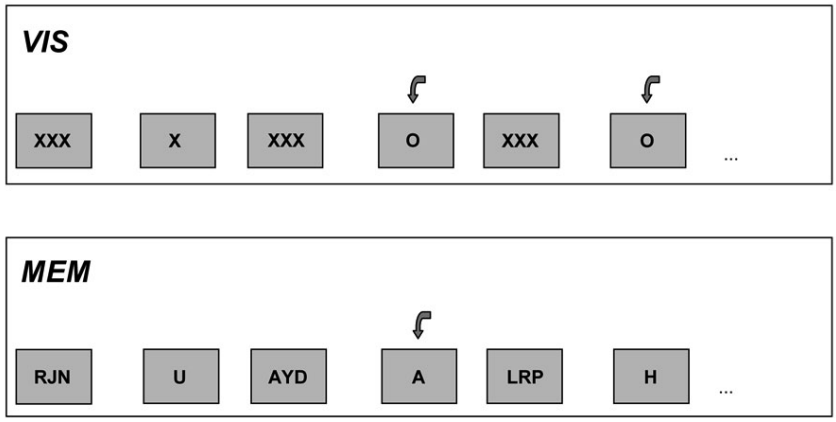


Fig. 7. (A) In the memory task (MEM) of the multimodal ERP study, three letters were presented and followed immediately by a single target letter. The subjects were instructed to push the button only when the target had been included in the previous set. (B) In the visual tasks (VIS), three symbols "XXX" were presented. The target symbol was either an "O" or an "X". The subjects were instructed to push the button only when seeing the target "O". =response with right hand.

The tasks were performed separately and in combination with each other (dual-task condition). In dual tasks, the stimuli of different modalities were presented concurrently so as to ensure an even distribution of auditory over visual stimuli to preclude any time-locked interference between the responses.

The study protocol consisted of seven task conditions in the following order: 1) AUD, 2) a training set for MEM, 3) MEM, 4) a training set for a dual task with AUD and MEM, 5) a dual task with AUD and MEM, 6) VIS, and 7) a dual task with AUD and VIS.

Each subject was sitting in a comfortable armchair 1.80 m from the screen in a quiet, semi-darkened room. During task performance, the research technician ensured that each subject had understood the tasks and stayed alert. In task conditions 1, 6, and 7, if the participants gave an incorrect response to the first three deviants, the performance was interrupted and the task explained again. In all tasks, reaction time, number of misses (no response in two seconds), and EEG activity were recorded.

Stimulations and EEG recording were done with a Cognitrace EEG/ERP system (Version 3.3, ANT, Enschede, Holland). EEG was recorded with active shielded 64-channel EEG caps with an electrode layout following the international 10-10 system (see Fig. 5) (Waveguard, ANT; electrode material Ag-AgCl) and with a DC-amplifier (REFA-64, ANT) using a sampling frequency of 512 Hz. Electro-oculography (EOG) and electrocardiography (ECG) were also recorded. Timing of the different stimuli and of the responses was recorded together with the EEG.

Pre-processing and analysis of the recordings was done with ASA software (Version 4.6.2.0, ANT). EEG was filtered with a bandpass of 0.3–30 Hz (12 dB/octave rollof). Blink artefacts were removed by an algorithm based on spatial filtering (240). The manually selected prototypes of blinks per recording numbered least ten. After artefact correction, the data were remontaged with a reference set to linked mastoids (M1+M2). Only data from electrodes Fp1, Fp2, Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, O1, and O2 were retained for further analysis. Remaining artefacts were excluded with an amplitude criterion of ± 75 μV before calculation of the averaged waveforms. The continuous EEG data was transformed off-line to 1100-ms epochs, starting 100 ms before the onset of each stimulus. Finally, the averaged waveforms were baseline corrected by the 100 ms preceding the stimulus as the baseline.

Amplitude and latency of P300 elicited by the auditory and visual stimuli were measured as the most positive waveform around 300 ms. In MEM, P300 was measured from the waveform elicited by the target letter included in the previously set of three letters. In VIS, P300 was measured from the waveform elicited by all "O" stimuli. The results of the automated peak detection were verified manually and corrections performed when necessary.

4.10 Statistical methods

Study I

The numbers and proportions of CSE cases and cases referred to FIOH as well as the measures of location and dispersion of the variables were calculated with Microsoft Office Excel 2007 (Microsoft Corp., Redmond, WA, USA). SAS 8.2 software (SAS Inc., Gary, NC, USA) served in the linear regression analyses and MedCalc Software Version 9.3.9.0 (MedCalc Software, Mariakere, Belgium) in the comparison of proportions with the Chi-square test.

Study II

In the MRI study, statistical analyses were performed with SAS 8.2 software. To study the association between MRI findings and solvent exposure we used logistic regression. The potential explanatory effects describing the exposure were DEY and OELY. Other factors incorporated in the analyses included patient age, amount of alcohol consumed, and number of cardiovascular risk factors.

Study III

In the EEG study, statistical analyses were performed with the GLM (General Linear Models) procedure in SAS 8.2 software. Because the distributions of absolute power values were right-skewed, we used logarithmic transformation. The models were adjusted for age. We used the traditional analysis of covariance which assumes that all categories have the same age dependence. No interactions of age and category

were detectable. Adjusted means and their 95% confidence limits were converted back to a non-logarithmic scale.

Study IV

In the auditory ERP study, the P300 latencies and amplitudes of CSE patients and laboratory controls were compared by use of an analysis of covariance with adjustment for age. Degrees of freedom were adjusted (Greenhouse-Geisser) when appropriate. The P300 values and neuropsychological performance between the study groups were compared by the independent measures t-test. The homogeneity of variances was evaluated with Levene's test. The associations of alcohol consumption, neuropsychological test results, and exposure indices with P300 values were studied by Spearman rank order correlation analysis. Comparisons between the subgroups of CSE patients were done with the independent samples t-test. In follow-up comparison of P300, we used the paired samples t-test. All statistical tests were two-tailed, and the level for significance was set at $p < 0.05$. The analyses were performed with the SPSS for Windows, version 12.0 (SPSS Inc., Chicago, IL, USA).

Study V

The comparisons of P300 values, task performance, and results in neuropsychological tests between CSE patients and matched controls were made by the independent measures t-test. The homogeneity of variances was evaluated with Levene's test. All statistical tests were two-tailed with the level of significance set at $p < 0.05$. The correlation of ERP values with neuropsychological test results was studied by Spearman rank order correlation analysis. The analyses were performed with the SPSS for Windows, Version 17.0. Missing amplitude values, i.e. when no P300 component was recognizable, were replaced with value zero. Latency values were not replaced, and thus the number of subjects was reduced in the AUD+VIS condition and no statistical testing was performed for the AUD+MEM condition.

5. RESULTS

5.1 Cases with suspected chronic solvent encephalopathy

Workers referred to FIOH during 1995–2005 for a suspicion of CSE numbered 425. The annual number of referrals (mean 38.6, range 26–47, SD 6.15) has remained rather constant (Fig. 8).

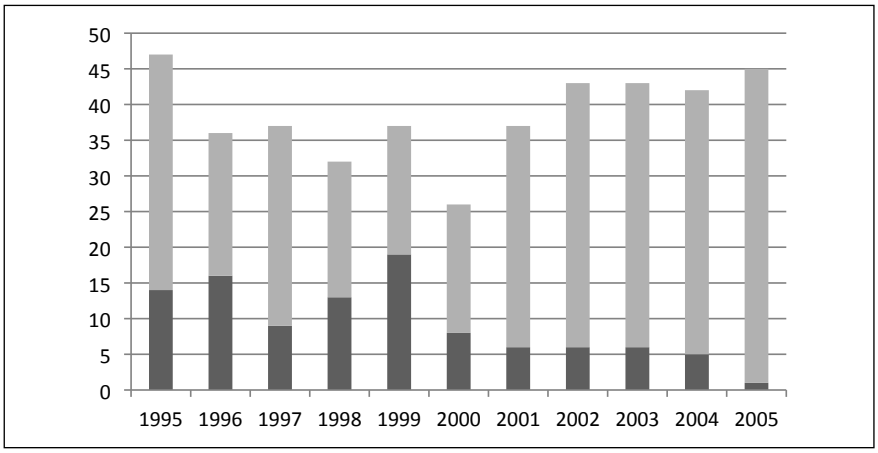


Fig. 8. Cases referred to FIOH with a suspicion of CSE annually, 1995–2005 (n=425). Each column's black segment represents the proportion of cases not diagnosed with CSE in that year but during following years.

Of the 425 referred cases, CSE was eventually diagnosed in 103 (24%). Comparing the time periods 1995–1999 and 2000–2005, the proportion of those diagnosed among referred cases declined from 38 to 15% (Fig. 8).

During 2002–2004, the referrals to FIOH (n=128) had come from occupational health care units in 71% of the cases, from a neurological outpatient clinic of a central or district hospital in 8%, from some other outpatient clinic in 10%, and from a rehabilitation unit in 8%. Three cases were found in a study project of construction painters at FIOH (14). Of the 128 cases, CSE diagnosis was rejected in 109 (85%). The most common reason: Of 109 cases in 47 (43%) the clinical picture or neuropsychological test profile was not suggesting CSE. Of these 47 cases, in 31 (66%), lifetime solvent exposure was considered insufficient to cause permanent CNS disturbances. In cases with multiple confounding etiologies, all with sufficient solvent exposure, the clinical picture or neuropsychological test profile or both may have suggested CSE, but even after follow-up and adequate treatment of confounding factors such as excessive alcohol consumption, depression, sleep apnea, or chronic pain, it was impossible to show that occupational solvent exposure was the main etiology (Table 5).

Table 5. Major reasons for rejection of chronic solvent encephalopathy diagnoses in suspected cases during 2002–2004 (n=109).

	n (%)
Clinical picture or neuropsychological test profile did not suggest CSE	47 (43)
Multiple confounding etiologies	22 (20)
Depression	21 (19)
Non-occupational brain disease	10 (9)
Psychiatric disease (other than depression)	4 (4)
Alcohol abuse	3 (3)
Sleep disorder	2 (2)

Of the cases referred to FIOH during 2002–2004, CSE was eventually diagnosed, not the year in which they were referred, but during the following years, in 19 of 128 (15%) cases; 14 (74%) of them due

to CSE were unable to perform any work. Of the five patients with residual work ability, four were never employed and were finally granted disability pensions. Only one patient continued in the same work but at lower exposure levels.

5.2 Cases with chronic solvent encephalopathy

During 1995–2007, cases diagnosed at FIOH with CSE as an occupational disease due to long-term solvent exposure numbered 128, including 12 women. The annual number of new cases diminished from 18 to 3 (Fig. 9). Most of the cases were diagnosed in southern and western Finland (Fig. 10).

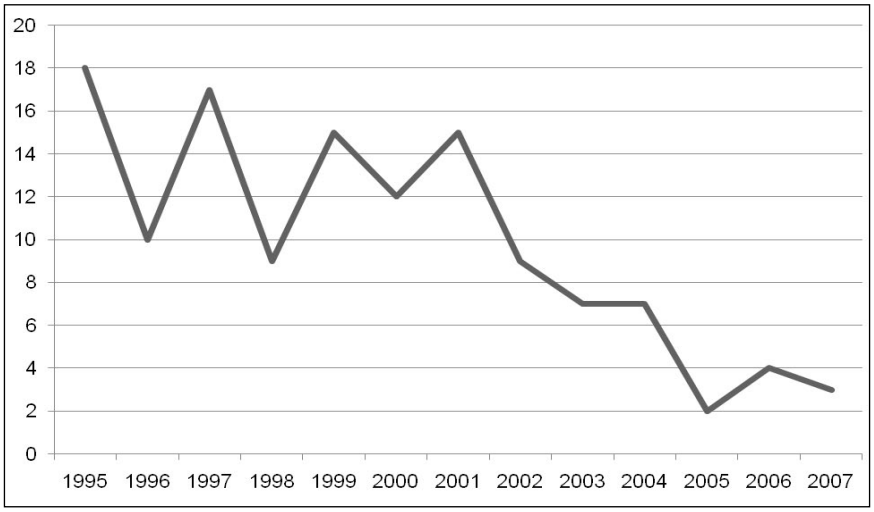


Fig. 9. Numbers of occupational chronic solvent encephalopathy cases in Finland diagnosed annually during 1995–2007 (n=128).

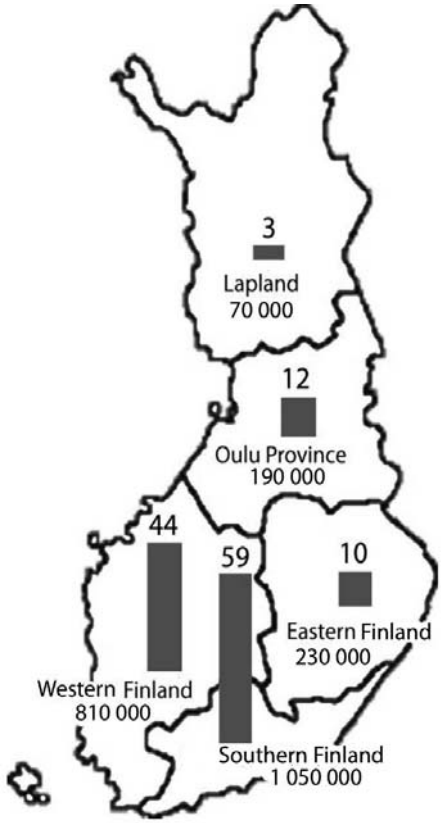


Fig. 10. Numbers of occupational chronic solvent encephalopathy cases during 1995–2007 and numbers of those employed in the five provinces of Finland.

Patients' mean age at diagnosis was 52.8 (median 54, range 35–73, SD 6.1); the majority (118 of 128) were ≥ 45. In classifying the cases according to the main work task, the youngest were the 11 (mean age 49.5) doing reinforced plastic lamination and the oldest were the 26 (mean age 54.7) construction painters. During 1995–2007, the patient age has increased annually by 0.6 years (p=0.0002, linear regression analysis).

5.3 Incidence of chronic solvent encephalopathy

Comparing the annual number of CSE cases to the number of employed, the incidence of CSE has decreased between 1995 and 2007 from 8.6 to 1.2 / million employed per year. During the study period, the mean incidence in different provinces ranged from 3.3 to 4.9 cases per million employed (mean 4.0), the lowest being in Lapland and the highest in Oulu Province.

Compared to the number employed in various work tasks, the average annual incidence of CSE during 1995–2007 was highest in wooden-surface finishers and in industrial, metal, or car painters, followed by floor layers and lacquerers (Table 6). Despite the second highest number of CSE cases in construction painting, this field was not among the tasks with the highest incidence figures.

Table 6. The main work tasks of the 128 chronic solvent encephalopathy (CSE) patients and incidence of CSE in relation to those employed

	n (%)[a]	Incidence[b]
Industrial, metal, or car painters	48 (38)	0.8
Construction painters	26 (20)	0.2
Printing-trade workers	12 (9)	0.3
Floor layers and lacquerers	11 (9)	0.7
Reinforced plastic laminators	11 (9)	0.3
Wooden surface finishers	9 (7)	0.9
Gluers	9 (7)	NA
Motor vehicle cleaners	8 (6)	NA
Other industrial workers	4 (3)	NA
Degreasers	4 (3)	NA
Rubber product workers	2 (2)	0.1
Footwear workers	2 (2)	< 0.1
Gasoline handlers	2 (2)	< 0.1
Vehicle and machine mechanics	2 (2)	NA
Maintenance and repair workers in industry	2 (2)	NA
Producers of paint, lacquer, and printing inks	2 (2)	NA
Laundry workers (dry cleaners)	1 (1)	0.1
Paint removers	1 (1)	NA

[a] Some had more than one main work task
[b] Average incidence during 1995–2007: CSE cases / 1000 workers in the work task under consideration according to the National Workforce Survey
NA=not available

Comparing the numbers of CSE cases, classified by main solvent exposure, with the numbers of exposed workers by agent in Finland, as retrieved from FINJEM, the incidence of CSE during 1995–2006 was highest in workers with exposure to aromatic hydrocarbons (decreased from 1.2 to 0.3 / 1 000 per year) and the group of other organic solvents (0.8–0.2 / 1 000 per year) (Table 7a). Compared with the number of workers exposed to levels above 50% of OEL, the incidence of CSE during 1995–2006 was highest in workers with exposure to aliphatic hydrocarbons (66.7–22.2 / 1 000 per year) (Table 7b).

Table 7a Incidence of chronic solvent encephalopathy (CSE) in Finland by solvent exposure

	1995–1997	1998–2000	2001–2003	2004–2006
Aliphatic and alicyclic hydrocarbons				
CSE cases[a]	8	8	6	2
Exposed workers[b]	12 000	10 000	10 000	11 000
Incidence[c]	0.2	0.3	0.2	0.1
Aromatic hydrocarbons				
CSE cases	43	33	25	12
Exposed workers	12 000	14 000	14 000	14 000
Incidence	1.2	0.8	0.6	0.3
Chlorinated hydrocarbons				
CSE cases	5	9	2	2
Exposed workers	5 100	3 000	2 400	2 400
Incidence	0.3	1.0	0.3	0.3
Other organic solvents[d]				
CSE cases	25	28	23	8
Exposed workers	11 000	12 000	10 000	11 000
Incidence	0.8	0.8	0.8	0.2

Table 7b Incidence of chronic solvent encephalopathy (CSE) in Finland by solvent exposure of the Finnish work force at levels >50 % of Occupational Exposure Limit Years

	1995–1997	1998–2000	2001–2003	2004–2006
Aliphatic and alicyclic hydrocarbons				
CSE cases[a]	8	8	6	2
Exposed workers[b]	120	90	30	30
Incidence[e]	22.2	29.6	66.7	22.2
Aromatic hydrocarbons				
CSE cases	43	33	25	12
Exposed workers	1 700	1 300	1 300	1 200
Incidence	8.4	8.5	6.4	3.3
Other organic solvents[d]				
CSE cases	25	28	23	8
Exposed workers	4 000	4 500	3 700	4 100
Incidence	2.1	2.1	2.1	0.7

[a] number of CSE cases with main exposure to the solvent group under consideration during the 3-year period
[b] data based on the Finnish Job-Exposure Matrix
[c] CSE cases annually / 1 000 workers exposed to the solvent group under consideration
[d] alcohols, ketones, esters, ethers, carbon disulfide, and glycol compounds
[e] CSE cases annually / 1 000 workers exposed at levels >50 % of OEL to the solvent group under consideration per year

5.4 Exposure-work of chronic solvent encephalopathy cases

CSE has occurred in a variety of work tasks, the most common being industrial, metal, or car painting, tasks entailing predominantly spray painting, and construction painting (Table 6). During 1995–2000, the number and proportion of all CSE cases have decreased among industrial, metal, or car painters: from 32 (40%) to 16 (34%) as well as among construction painters: from 18 (22%) to 8 (17%). The number of printers, floor layers and lacquerers, and reinforced plastic laminators remained constant at six, but their proportion of all CSE cases increased from 6 to 13%.

5.5 Solvent exposure of the chronic solvent encephalopathy cases

According to FINJEM, the number of workers with exposure to aliphatic hydrocarbons, chlorinated hydrocarbons, and other organic solvents (alcohols, ketones, esters, ethers, carbon disulfide, and glycol compounds) decreased from the 1960s to the 1990s about 60% and with exposure to aromatic hydrocarbons, about 43%. The proportion of workers exposed to levels >50% of OEL has decreased among those with exposure to aliphatic (from 1.9 to 0.6%) and to aromatic hydrocarbons (from 18 to 11%) but increased among those exposed to other organic solvents from 12 to 37%.

The mean DEY of the patients was 28.4 (median 28, S.D. 8.3, range 7–49), and the mean OELY, 10.5 (median 9, S.D. 4.3, range 4–26). CSE cases with DEY below 10 numbered 2, whereas in most cases, among 128, for 112 (88%), DEY was ≥ 20. The lowest mean DEY (23.8) was among the 11 reinforced plastic laminators who also had the highest mean OELY (14.1). The mean DEY (32.9) of the 26 construction painters was the highest, and their mean OELY the lowest (10.0) (Fig. 11).

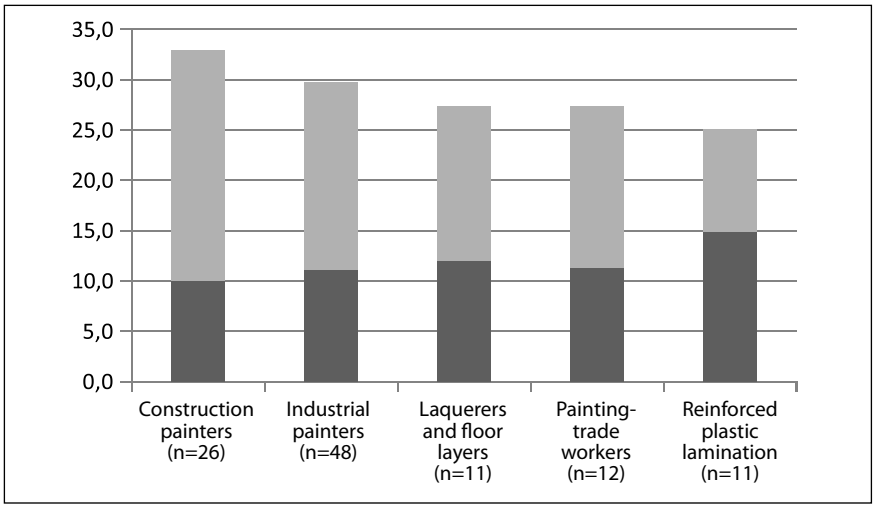


Fig. 11. Mean duration of occupational solvent exposure in years in the five most common work tasks of chronic solvent encephalopathy patients in Finland during 1995–2007.The black segment in the column represents mean occupational exposure limit years (OELY).

OELY was less than six in four patients. Two of them, a process worker (DEY 7, OELY 4) and a supervisor (DEY 19, OELY 5) with exposure peaks mainly to xylene, n-propanol, and possibly to methylene chloride, shared the same workplace in the pharmaceutical industry. In its entirety, the lifetime exposure of another supervisor in industrial painting with exposure to mainly xylene (DEY 23, OELY 5) was considered sufficient to cause CNS disturbances. The exposure levels of a gluer in furniture manufacture (DEY 9, OELY 4.5) were considered relatively low, but skin exposure had been estimated as considerable, and previous reports from similar work tasks suggest exposure levels higher than these.

During 1995–2007, DEY increased annually by 0.8 ($p=0.0003$, linear regression analysis), but OELY – an estimate of intensity of lifetime exposure – remained similar ($p=0.92$).

The most common main solvent exposure, in 100 (78%) of 128 cases, had been to aromatic hydrocarbons, especially to solvent mixtures containing toluene and xylene (Table 8). The main exposure in 85 (66%) cases included other organic solvents (alcohols, ketones, esters, ethers, carbon disulfide, and glycol compounds), in 60 (47%) mineral spirits, in 24 (19%) aliphatic hydrocarbons, and in 19 (15%) cases chlorinated hydrocarbons (Table 8).

The most common exposure of construction painters, in 25 (96%) of 26 cases, was to mineral spirits, whereas all the 48 industrial, metal, or car painters had been exposed to mixtures of aromatic hydrocarbons; the most common component, in 44 of 48 cases (92%), was xylene. Among 11 who did reinforced plastic lamination, the main exposure in 10 (91%) was to styrene (Table 8).

Most of the 128 patients, 118 (92%), had been exposed to mixtures of solvents. Patients with single solvent exposure had been exposed to styrene, toluene, xylene, trichloroethylene, perchloroethylene, or ethyl acetate.

Table 8. Main solvent exposure of the 128 chronic solvent encephalopathy cases and of the cases performing the five most common work tasks.

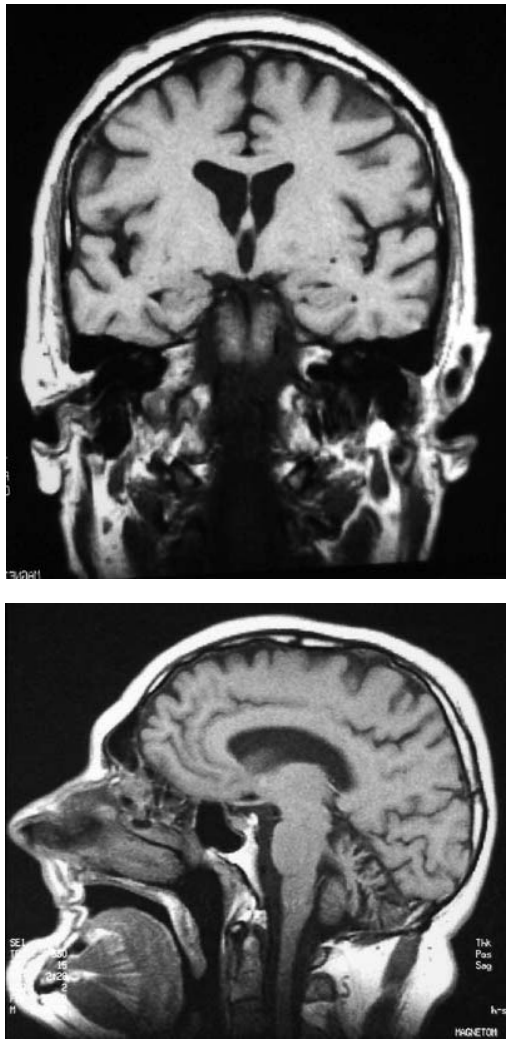
	All patients[a]	Industrial, metal, or car painting[b]	Construction painting[b]	Printing work[b]	Floor laying and lacquering[b]	Reinforced plastic lamination[b]
Number of patients n (%)	128 (100)	48 (38)	26 (20)	12 (9)	11 (9)	11 (9)
Solvents						
Aliphatic hydrocarbons	24 (19)	2 (4)	2 (8)	2 (17)	6 (55)	1 (9)
n-hexane	14 (11)					
Other	22 (17)					
Aromatic hydrocarbons	100 (78)	48 (100)	17 (65)	6 (50)	8 (73)	10 (91)
Toluene	68 (53)	29 (60)	10 (38)	5 (42)	7 (64)	3 (27)
Xylene	65 (50)	44 (92)	12 (46)	1 (8)	4 (36)	4 (36)
Styrene	22 (17)	14 (29)	1 (4)	0 (0)	2 (18)	10 (91)
Benzene	2 (2)	0 (0)	0 (0)	2 (17)	0 (0)	0 (0)
Other	11 (9)	7 (15)	0 (0)	1 (8)	0 (0)	0 (0)
Mineral spirits[c]	60 (47)	27 (56)	25 (96)	4 (33)	3 (27)	2 (18)
Chlorinated hydrocarbons	19 (15)	4 (8)	3 (12)	2 (17)	0 (0)	3 (27)
Trichloroethylene	7 (5)					
Perchloroethylene	4 (3)					
Trichloroethane	3 (2)					
Methylene chloride	8 (6)					
Other	1 (1)					
Other organic solvents	85 (66)	35 (73)	5 (19)	10 (83)	8 (73)	4 (36)
Alcohols						
Methanol	1 (1)					
Ethanol	17 (13)					
Propanol	18 (14)					
Butanol	34 (27)					
Ketones						
Acetone	33 (26)					
Methyl ethyl ketone	9 (7)					
Other	7 (5)					
Esters						
Ethyl acetate	29 (23)					
Other	34 (27)					
Ethers	5 (4)					
Glycol compounds	25 (20)					
Gasoline	1 (1)					
Organic nitrogen compounds	1 (1)					

[a] 118 of 128 cases had their main exposure to more than one solvent
[b] only main exposure classes included except for aromatic hydrocarbons
[c] mainly White spirit or Stoddard Solvent, a mixture of aliphatic hydrocarbons with a maximum of 25% of aromatic hydrocarbons

5.6 Magnetic resonance imaging

Of 71 CSE patients, the brain MRI of 27 (38%) was classified as abnormal – as atrophy or abnormal white matter findings or both. Of these 27 patients, 10 had both atrophy and abnormal white matter findings. Of 71 patients, 17 (24%) had brain atrophy in any brain area, with the most common locations being for 9 in the cerebellar cortex and for 7 in the vermis. Only one patient had vermian atrophy without cerebellar atrophy. Central cerebellar atrophy was present in four and corpus callosum atrophy in three patients. The majority of the cerebral atrophy findings were located in the frontal and parietal brain areas (five cases each). The mean atrophy score reflecting extent of atrophy was 2.6 (range 1–8). Brain atrophy findings are shown in Fig. 12. Of 71 patients, abnormal white matter hyperintensities were visible in 20 (28%), for whom the most prevalent abnormalities were small (in 14) and large (in 12) focal lesions in the deep white matter. Focal confluent lesions were present in three and diffuse confluent lesions in one patient. White matter lesions were visible in the brainstem of seven patients. Examples of white matter findings are in Fig. 13.

Cerebral and cerebellar brain atrophy was, unrelated to age, associated with duration of exposure (P_e 0.009 and 0.017, respectively). Patients whose exposure duration had been 10 years longer were from three to four times more likely to have atrophy (1.140^{10}=3.7, 1.116^{10}=3.0) than were those with shorter exposure. Periventricular and brainstem white matter hyperintensities were related to age (P_e 0.04 and 0.03, respectively), and vermian atrophy to alcohol consumption (P_e 0.02).



(A)

(B)

Fig. 12. Coronal (A) and sagittal (B) sections of the brain MRI of a 54-year-old painter revealed in T_1 -weighted images central and cortical brain atrophy in frontal, parietal, and occipital brain areas and in the cerebellum and vermis. Atrophy sum score was 6. The patient had hypertension and hypercholesterolemia, he was a smoker, and his average alcohol consumption was 480 g/month. He had been exposed mainly to White spirit and xylene for 40 years (OELY 10).

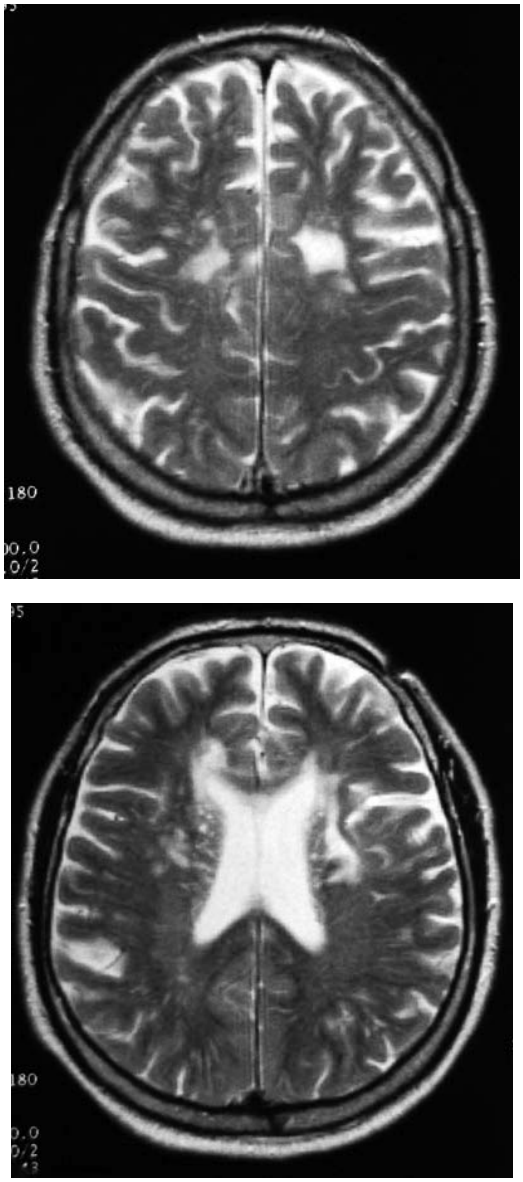


Fig. 13. Axial sections of the brain MRI of a 58-year-old supervisor in the cleaning and degreasing industry reveal small and large focal lesion in deep white matter and large frontal capping and irregular lining in periventricular white matter in T_2 -weighted images. The patient had been exposed mainly to trichloroethylene for 43 years (OELY 8), he had no other diseases, he did not smoke, and his average alcohol consumption was 39 g/month.

5.7 Quantitative electroencephalography

In the QEEG study, the power of the theta band in the frontal area was 1.6 times higher in the CSE patient group than in the laboratory control group (mean 4.7 $(\mu V)^2$, 95% Cl 4.0–5.5 versus mean 3.0 $(\mu V)^2$, 95% Cl 2.6–4.2; p=0.019). Compared to the age-matched control group, CSE patients had lower beta power in the centroparietal area (mean 6.3 $(\mu V)^2$, 95% Cl 5.6–7.1 versus mean 4.8 $(\mu V)^2$, 95% Cl 4.1–5.7; p=0.009), but theta power did not differ. No differences appeared, however, in beta power between CSE patients and laboratory controls. The age-matched controls had increased beta power compared to the laboratory controls in all except the occipital area.

The variables of solvent exposure (DEY, OELY, and the ratio OELY/DEY) did not associate with the power of theta activity in the frontal area. A weak negative correlation emerged in the CSE patient group between frontal theta power and amount of reported alcohol consumption. In the age-matched control group, amount of reported alcohol use showed no association with increased theta or beta power.

Of the 47 QEEG recordings for CSE patients, 5 (11%) were originally interpreted as abnormal. A diffuse increase in slow activity was evident in four recordings, and focal slow activity in the right parieto-occipital region in one recording.

5.8 Auditory event-related potentials

The P300 amplitude of the auditory ERP at Pz was smaller in the patient group (mean 7.5 μV; SD 3.6) than in the laboratory control group (mean 11.8 μV; SD 4.1; $F(1,167)=24.4$; $p<0.001$, 95% CI -4.4 to -1.8) or in the age- and education-matched control group (9.0 μV; SD 4.0; p=0.007, 95% CI -2.6 to -0.4). P300 latency was longer in the patient group (mean 358 ms; SD 28) than in the laboratory control group (mean 339 ms; SD 19, $F(1,167)=7.6$, p=0.006, 95% CI 3.12 to 18.7) but did not differ from that of the matched control group (mean 358 ms; SD 22; p=0.947, 95% CI -7.4 to 6.9). Age correlated negatively (-0.394, $p<0.001$) with amplitude and positively (0.417, $p<0.001$) with latency of P300.The exposure indices DEY and OELY did not correlate with

P300 amplitudes (-0.06, p=0.585) or latencies (0.009, p=0.932). Nor did major depression nor use of CNS medication associate with P300 amplitudes or latencies within the patient group, nor did the amount of alcohol consumed in the patient' or in the matched control groups.

Digit symbol substitution correlated positively with P300 amplitude both in the patient group (0.279, p=0.011) and in the matched control group (0.220, p=0.026). Digits forward had a tendency to correlate positively with the P300 amplitude in the CSE patient group (0.20, p=0.074) but not in the matched control group (0.017, p=0.864). Digits backward correlated with amplitude in neither group. P300 latency correlated with none of the three neuropsychological tests in either group. The neuropsychological test results did not associate with major depression, amount of alcohol consumed, or exposure indices.

The follow-up group of 19 patients showed no significant changes in their P300 latency or amplitude values between their first and the second ERP recording (mean time between the recordings was 14 months, range 10–18). The P300 amplitude improved in four patients, deteriorated in four, and remained unchanged in eleven when an at least 25% change in amplitude was the criterion for improvement or deterioration. No obvious difference in age, DEY, or OELY appeared between patients with improved or deteriorated amplitude. It seemed, however, that the exposure-free time had been longer for the four patients with improved P300 amplitude than for the four patients with deteriorated amplitude. All the changes in P300 latency values were less than 25%.

All the amplitudes in the CSE patient group and in the matched control group were classified as normal (i.e. age corrected mean ± 2.5 SD) against the laboratory's reference values. The latencies in 30% of the CSE patients and in 26% of the matched controls were classified as abnormal.

5.9 Multimodal event-related potentials

Single-task conditions

The P300 amplitude in the AUD task at Pz was smaller in the patient group (mean 4.3 μV; 95% CI 2.6 to 6.0) than in control group (mean 7.5 μV; 95% CI 5.4 to 9.5; p=0.034). Amplitudes between groups at Fz

did not differ, nor did P300 amplitude differ in VIS or MEM tasks (Fig. 14). P300 latency in any single-task condition did not differ significantly between groups.

Dual-task conditions

The auditory P300 component in the AUD+VIS condition was recognizable in 3 of 11 patients and in 12 of 13 controls. In the AUD+MEM condition, the auditory P300 component was present in 1 of 11 patients and in 9 of 13 controls.

In the entire study population, the auditory P300 amplitude in the single condition was smaller in the 9 subjects without recognizable auditory P300 in the AUD+VIS condition (mean 4.0 μV, 95% CI 1.9 to 6.1) than in those 15 with recognizable auditory P300 (mean 7.2 μV, 95% CI 5.5 to 9.0; p=0.03).

In the AUD+VIS condition, mean auditory P300 amplitude was decreased in the patient group (mean 1.2 μV; 95% CI 0.0 to 2.5) compared to the control group (mean 4.5 μV; 95% CI 3.2 to 5.8, p=0.002). In the AUD+MEM condition, the results were similar: patient group (mean 0.5 μV; 95% CI -0.4 to 1.3) versus the control group (mean 2.6 μV; 95% CI 1.3 to 3.9; p=0.016) (Fig. 15).

Between groups, the mean change in the auditory amplitude values from AUD to AUD+VIS (mean 3.1 μV, 95% CI 1.0 to 5.1 in patients and mean 3.0 μV, 95% CI 1.4 to 4.5 in controls; p=0.94) and from AUD+VIS to AUD+MEM conditions (mean 0.8 μV, 95% CI -0.4 to 1.9 in patients and mean 1.9 μV, 95% CI 0.9 to 2.9 in controls; p=0.16) did not differ.

The visual P300 amplitude in the AUD+VIS or AUD+MEM conditions and the P300 latency in the AUD+VIS condition did not differ between the groups (Fig. 14).

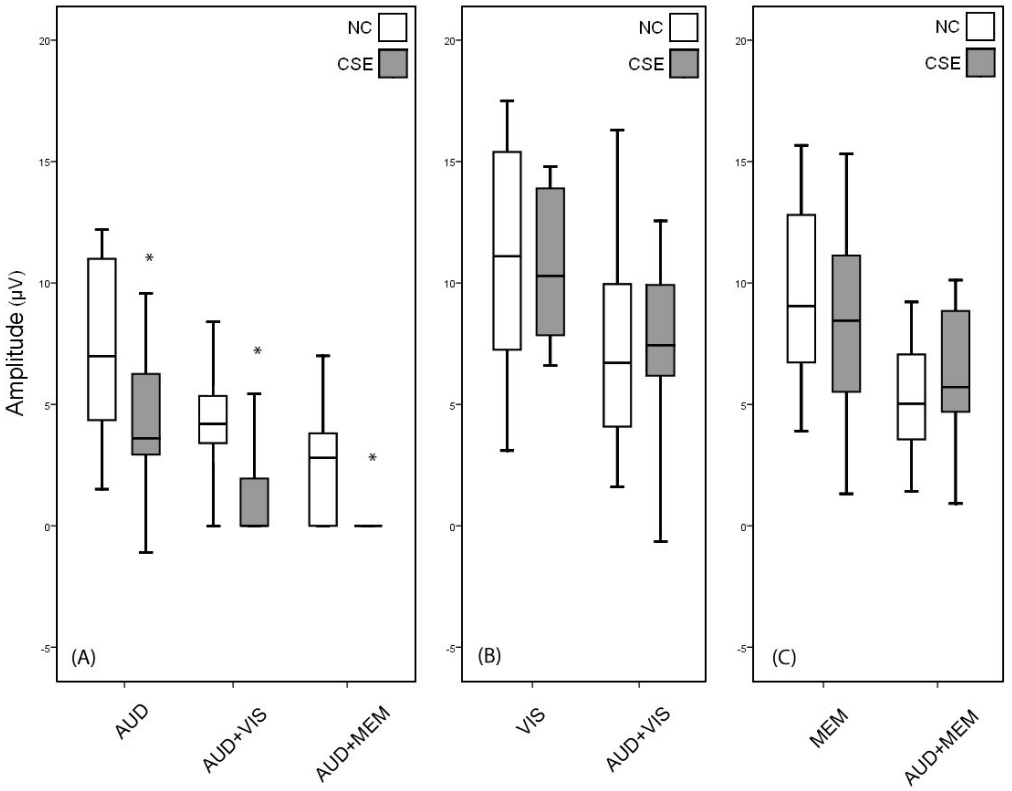


Fig. 14. Median, first and third quartile, minimum and maximum of P300 amplitude values from (A) auditory targets in single condition (AUD) and dual conditions (AUD+VIS, AUD+MEM), (B) visual targets in single condition (VIS) and dual condition (AUD+VIS), (C) visual targets in MEM in single condition (MEM) and dual condition (AUD+MEM). AUD=auditive task, VIS=visual task, MEM=memory task, CSE= patients with chronic solvent encephalopathy, NC=normal controls, *=p<0.05.

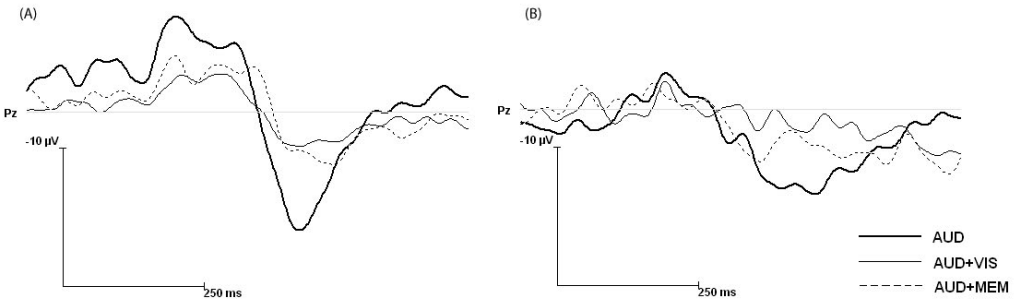


Fig. 15. Auditory event-related potentials at Pz in single and dual-task conditions of (A) a control and (B) a CSE patient. An unrecognizable P300 response in the patient in the AUD+MEM dual-task condition. AUD = auditive task in single condition, AUD+VIS = auditive and visual tasks in dual condition, AUD+MEM = auditive and memory tasks in dual condition.

Task performance

Reaction times (RT) in single-task conditions for auditory targets, visual targets, or responses in the memory task did not differ between groups. In both dual-task conditions, RT for auditory targets were longer in the patient group (AUD+VIS mean 525 ms; 95% CI 481 to 569 ms; AUD+MEM mean 606 ms; 95% CI 552 to 661ms) than in the control group (AUD+VIS mean 451 ms; 95% CI 425 to 476 ms; p= 0.006, 95% CI 23 to 126; AUD+MEM mean 531 ms; 95% CI 496 to 566 ms; p= 0.028, 95% CI 9 to 142). RT for the visual target was prolonged in the patient group (AUD+ VIS mean 701 ms; 95% CI 636 to 766 ms) compared to that in the control group (AUD+ VIS mean 606 ms; 95% CI 567 to 644 ms; p= 0.017, 95% CI 19 to 172) (Fig. 16).

Response accuracy was lower in the patient group in all tasks, but the individual variation was large, and differences compared to the control group were statistically nonsignificant. In the neuropsychological tests, significant differences between patients and controls appeared in the number of stages completed (mean 6.4, 95% CI 4.6 to 8.1 and mean 8.6, 95% CI 8.2 to 9.1; p=0.03) and in adjusted total errors (mean 78.2, 95% CI 39.4 to 117.0 and mean 30.6, 95% CI 19.4 to 41.9; p=0.04) in IED.

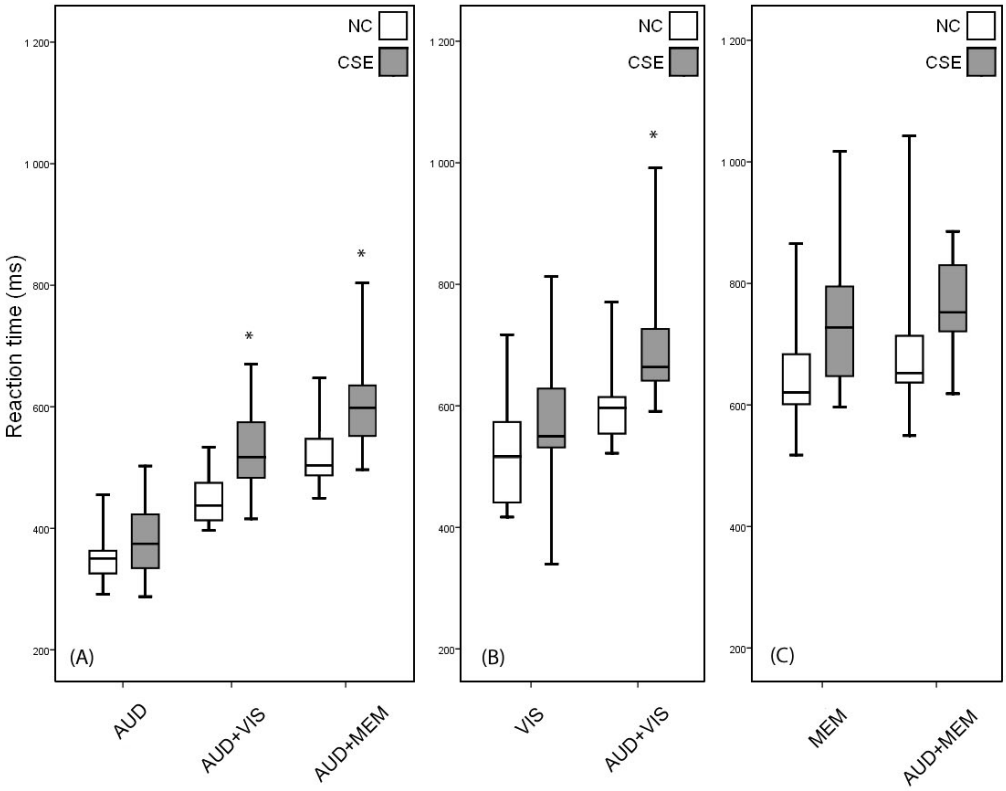


Fig. 16. Median, first and third quartile, minimum and maximum of reaction time values for (A) auditory targets in single condition (AUD) and dual conditions (AUD+VIS, AUD+MEM), (B) visual targets in single condition (VIS) and dual condition (AUD+VIS), (C) visual targets in MEM in single condition (MEM) and dual condition (AUD+MEM). AUD=auditory task, VIS=visual task, MEM=memory task, CSE= patients with chronic solvent encephalopathy, NC=normal controls, *=p<0.05.

6. DISCUSSION

6.1 Referred and diagnosed chronic solvent encephalopathy cases

Number of cases and incidence of CSE

The number and incidence of CSE cases in Finland during 1995–2007 have clearly diminished, but the annual number of referrals to FIOH of cases with suspected CSE has remained rather constant. The number of CSE cases in the five provinces of Finland has varied, largely reflecting differences in population, work force, employment, and business structure. That local incidence figures were, however, rather equal indicates that knowledge and detection of solvent-exposure-related CNS adverse effects as well as screening of solvent exposed workers have spread widely across the country.

This decrease in Finnish CSE cases during 1995–2007 is congruent with the trend observed during 1997–2006 in the Netherlands (180). Moreover, the declining trend in the incidence figures during 1980–1998 reported in the European survey has continued in Finland (2). Legislative action and cooperation between trade unions and employers has enabled the prevention of solvent-related adverse effects (1,13). During recent last decades, the number and proportion of solvent-exposed workers and the levels of solvent exposure in many occupations have decreased (12). Nowadays, over 70% of the paints and lacquers in construction painting are water-soluble (10,11). The active replacement of chemicals by less harmful ones is reflected in the decreasing proportion of workers exposed to aliphatic, aromatic, and halogenated hydrocarbons at levels above 50% of OEL. The increased age and DEY of CSE patients between 1995 and 2007 while OELY has remained unchanged indicates slower CSE devel-

opment at lower exposure levels. The occupational solvent exposure of most of the CSE patients (118 of 128, 92%) diagnosed between 1995 and 2007 had begun in the 1960s and 1970s, when workers´ solvent exposure was more extensive (12). As the working conditions, protection, and chemical composition of the products have improved since the 1980s (11), the number and incidence of CSE cases will presumably further decline, but only if the current control of solvent exposure continues.

The number and incidence of CSE cases may, however, be somewhat higher than now reported. This is supported by the study on symptom screening in solvent- exposed populations which revealed unrecognized CSE cases (14). OHS usually performs the screening, which is reflected in the high proportion of referrals (71%) to the FIOH from OHS. In Finland, OHS covers nearly 90% of employees. For the self-employed – including many solvent-exposed workers – OHS is, however, voluntary. In 2004 the coverage was only 16% (241). This highlights the importance of widespread knowledge among health care professionals, also other than those at OHS, on the health effects of occupational solvent exposure.

The rather constant number of referrals during 1995–2005 – despite the decreased incidence of CSE – reflects improved awareness among workers and health care professionals of the health effects of occupational solvent exposure and effective symptom screening of exposed workers. The lowered threshold for recognizing symptoms indicating CSE and initiating investigations may have led, however, to a higher number of referred cases with etiologies other than solvent exposure. This is unsurprising, because the symptoms, such as sleep and mood disturbances, difficulties in concentration, and complaints about memory, are non-specific and are common in the general population. This is reflected in the high proportion of rejected cases with a clinical picture or neuropsychological test profile not indicating CSE (43% of all rejected cases), even though the life-time solvent exposure in 34% of those cases was considered sufficient to cause CNS adverse effects. This highlights the importance for the accuracy of diagnosis of profound multidisciplinary diagnostics with evaluation and treatment of other etiologies as well as thorough follow-up. Improved understanding of the characteristics of CSE and the relevance of sleep (219) and mood disorders (216) in the differential diagnostics may have, however, resulted in an increase in the proportion of cases where factors other than solvent exposure are

considered to be the main etiology (in 44% of the rejected cases). This may in part explain the decreased number of CSE cases, although the diagnostic procedure and criteria per se have remained unchanged. The earlier detection of symptoms and milder cognitive disturbances upon diagnosis has added to the diversity of etiological factors that must be taken into account in the differential diagnostics of CSE. Change in the evaluation of etiological alternatives is evident when considering the study from 1998 which reported only alcohol or drug abuse, head injury, and cerebrovascular or other neurological diseases as the reasons for exclusion from CSE diagnosis (8).

The incidence of CSE in Finland during 1995–2007 fell from 8.6 to 1.2 patients per million employed. In the previous study estimating the incidence of CSE in Europe, the incidence in 1997 ranged from 0.1 to 16.8 patients per million employed (8.5 in Finland) (2). This is fairly congruent with the incidence figures in the mid-nineties reported here. We were able to estimate the incidence of CSE also in populations at risk, meaning to compare the number of CSE cases to the number of those employed in various work tasks with solvent exposure and to the number of workers exposed to specific solvent groups at various exposure levels. Comparison of the number of CSE cases classified by their main solvent exposure with national data from FINJEM on the exposed workforce revealed the highest incidence in workers whose exposure had included aromatic hydrocarbons or solvents from the group of other organic solvents or both. The comparison to a workforce exposed at levels >50% of the OEL revealed the highest incidence in workers with their main exposure to aliphatic hydrocarbons. The incidence figures in these highly exposed populations are especially relevant because the exposure levels of all our CSE patients have exceeded 50% of the OEL. These results may thus indicate the underrated neurotoxicity of aliphatic hydrocarbons.

Exposure-work tasks

The exposure-work tasks associated with CSE in our study are very similar to those reported from New Zealand (8,17) and from the Netherlands (180). The most common work task of the CSE patients diagnosed in the 1990s was painting. In the 2000s other work tasks, such as printing, floor laying and lacquering, and reinforced plastic laminating, have emerged.

Early solvent studies focused primarily on painters, which presumably led to a decrease in solvent exposure in construction painting, among the first occupations affected. As over 70% of the paints and lacquers in construction painting are nowadays water-soluble, the percentage used in industrial painting is only 10 (10,11). The relative increase in number of CSE cases in, for example, wooden-surface finishing and industrial, metal, or car painting may thus reflect inadequate preventive actions and a need for focus on information and screening. Furthermore, younger age at CSE diagnosis, shorter mean DEY, and higher OELY in reinforced plastic lamination, with exposure predominantly to styrene, suggests an increased risk for CSE in this field.

Solvent exposure

The most common solvent exposure (aromatic hydrocarbons and the group of other organic solvents) among the CSE cases in our study is in line with that reported in New Zealand (8), although due to a different classification of solvents, so detailed comparison is unfeasible. In one of the cases with single-solvent exposure, the patient was exposed to ethyl acetate, considered to have low neurotoxicity at occupational exposure levels (242). In rats, however, subchronic exposure at high levels causes neurobehavioral disturbances (243). More attention should thus be on the occupational exposure levels and neurotoxic effects of ethyl acetate; it was, among our 128 CSE patients, also a component in the solvent mixture in 28 (22%) cases.

The duration of occupational solvent exposure in our patients was almost always more than 10 years and in most cases exceeded 20. DEY of at least 10, also suggested by the expert group convened by the European Commission (187), seems to be a good practical guideline for evaluation of exposure in suspicion or in diagnosis of CSE. OELY is a more accurate index of the neurotoxicity of solvent exposure. It seems useful in the diagnostics of CSE, although its estimation requires expertise in and detailed knowledge of working conditions, solvent exposure, and exposure levels. OELY is, however, a retrospective estimate relying on the history of life-time solvent exposure and on data for exposure levels in similar work tasks. It is thus prone to inaccuracy; it may under- or overestimate individual exposure, especially exposure peaks. Our four

CSE cases with OELY values between four and six indicate that the lower limit of six, usually considered a prerequisite for a CSE diagnosis at FIOH (14), should be merely a guideline. Based on our results, an OELY above six can be considered sufficient for the diagnosis of CSE, at an OELY between four and six the diagnosis is possible, and below four, the exposure is probably insufficient to cause CSE. While the mean age and DEY of CSE patients have increased between 1995 and 2007, mean OELY has remained unchanged, which indicates an OELY threshold for CSE.

Patient characteristics

Our patients' mean age (52.8 years), as well as mean duration of exposure (28.4 years) was clearly higher than reported in New Zealand (mean age 39.0 years, mean exposure 19.8 years) (8). They also found cases aged less than 30, whereas in our study population, no CSE appeared in workers aged less than 35, and most of the cases were over 45. The difference in age and duration of exposure may on the one hand be related to the study design in New Zealand, where medical practitioners actively screened workers during 1993–1997, which may have led to earlier diagnosis at a younger age. On the other hand, higher exposure level may contribute to diagnosis at a younger age. The patients may also present with milder brain disease, as did 14 (18%) of the 76 presenting with CSE type I, which in Finland is actually not considered CSE due to lack of cognitive findings.

Almost all the patients referred to FIOH during 2002–2004 (14 of 19; 74%) were considered unable to work and granted a disability pension due to CSE. Of the five patients with residual work ability, four were finally granted a disability pension, and only one continued in working life. Employment of workers with residual work ability often fails, due to restrictions on their solvent exposure, and cognitive disturbances may prevent occupational rehabilitation. To maintain solvent-exposed workers' ability to work, we should intensively focus on prevention of excessive exposure, early detection of symptoms predicting CSE, and on sensitive and valid tools for early diagnostics.

6.2 Magnetic resonance imaging

MRI is included in the diagnostic procedure of CSE at the FIOH and in many other centers at least in Europe, the United States, and New Zealand (6). Because MRI findings among studies have, however, been inconsistent, the role of MRI as a diagnostic method has been unclear.

Of 71 CSE patients, we found slight to moderate MRI abnormalities in 27 (38%). The most prevalent white matter abnormalities were small or large focal lesions in the deep white matter. Atrophy was most frequently located in the frontal or parietal cortex, vermis, and cerebellum.

Our slight white-matter findings and brain atrophy are congruent with the results of other MRI studies on CSE patients (66,70). Findings of thinning of the corpus callosum and hypointensity in the basal ganglia in T_2 -weighted images in solvent-exposed workers or CSE patients (70,72,74) – similar to that associated with toluene or alcohol abuse (26,41,42,50) – were not corroborated here. It thus remains unclear whether these findings would be explained by solvent exposure or by some other etiology.

Most frequently, cerebral atrophy occurred in frontal and parietal brain areas. This is in line with the assumption of frontoparietal dysfunction in CSE which is supported by SPECT studies on solvent-exposed workers and CSE patients (127,203,244). Furthermore, PET in solvent-exposed workers with cognitive dysfunction has, during a working-memory task, revealed frontal dysfunction (164).

MRI studies have shown that alcohol abuse and even moderate alcohol consumption is associated with brain atrophy (53–55). This is observed in the cerebellum, especially in the upper vermis, and in the frontal white-matter. A frequent finding is also global volume loss (245–247). We found an association between alcohol consumption and vermian atrophy but not cerebellar or cerebral atrophy. Excessive alcohol consumption was an exclusion criterion, but if alcohol consumption was under-reported, it would be impossible to totally exclude the effects of alcohol on MRI findings. Since, alcohol (i.e. ethanol) is itself a solvent, similarity in brain MRI findings in association with alcohol abuse and solvent exposure would be unsurprising.

Brain atrophy is also associated with age (248), but we found no such association. Cerebral and cerebellar atrophy was, however, associated with duration of exposure even with age as a covariate in statistical analyses. This confirms findings in solvent-exposed workers of an association between duration of solvent exposure and brain atrophy (249).

Most of our findings in the white matter were considered to be normal age-related changes or only slight abnormalities. In a normal healthy population, age-related white matter hyperintensities become increasingly apparent after age 50 (250), and we found an association between periventricular and brainstem white matter hyperintensities and age. As we lacked a control group, it is difficult to conclude whether or not CSE patients have more brain MRI abnormalities, atrophy, or white matter changes than do healthy non-exposed subjects of the same age.

Most (62%) brain MRI scans of our CSE patients were classified as normal. Our percentage of abnormal MRI was much lower (38%) than in earlier MRI studies (70% – 100%) (66,70). This difference may be due to the thorough diagnostic and differential diagnostic procedure and follow-up at FIOH, and strict criteria in the MRI study to exclude cases with confounding etiologies. Moreover, as we wanted to avoid overestimation of the MRI abnormalities, the finding was considered positive only if both neuroradiologists agreed; if disagreement occurred, the lower rating was chosen. Visual rating is always subjective, and interobserver variability increases as the findings diminish. Accuracy of evaluation of brain atrophy can be improved by volumetric methods. Visual evaluation is, however, the method used in clinical practice. Our study, as any other previous studies, revealed no specific MRI findings in CSE. Judgment as to the presence and etiology of MRI findings in cases with a suspicion of CSE should be cautious: In cases with major abnormalities in brain MRI, non-solvent etiologies deserve consideration.

6.3 Quantitative electroencephalography

QEEG in CSE patients – compared to that in laboratory controls – revealed an increase in absolute frontal theta power indicating neuronal dysfunction in frontal areas. In the study of Ørbæk et al, increased theta power appeared in all brain areas of CSE patients, although the relative

increase in absolute theta power was most prominent in frontal areas (132). This difference may be explained by a milder brain disorder in our patients (diagnosis in the 1990s) due to lower exposure levels than the levels for patients of the previous study (diagnosis in the 1970s).

The laboratory controls in our study were younger, but age was controlled for in the statistical analyses and did not interfere with the results. As the laboratory controls, recruited from the staff of FIOH, were probably better educated than the patients, we used another control group, comprising age-matched blue-collar workers of the same socio-economic and educational level as the CSE patients.

In comparison with CSE patients, these matched controls presented with increased beta power in their temporal areas. Compared to the laboratory control group, absolute frontal theta power was increased in the age-matched control group almost as much as in the CSE patient group (1.5 versus 1.6 times), and beta power was increased in all except occipital areas. In conditions of reduced cognitive processing capacity such as in aging and in pathological conditions such as in alcohol encephalopathy and Alzheimer's disease, theta frequency increases (123,124). In the original study of Portin et al, one-fifth of the matched controls presented, however, with mild cognitive impairment on cognitive tests (228). The authors stated that "the causes of this impairment and possible incipient cerebral dysfunction were not easily recognizable on the basis of health data or employment status and thus remained unexplained" (228). We did not, however, find any association between cognitive scores and EEG findings.

The increase in total or beta power seen in solvent-exposed workers and CSE patients (69,115,116,130,132–134) remained unconfirmed here. Increased beta power, as well as increased frontal theta power, associates with alcohol abuse and also with moderate alcohol consumption (125,251). Interestingly, the only characteristic difference was in alcohol consumption between matched controls (381.2 grams absolute alcohol / month) and CSE patients (205.2 grams). We found, however, no association between theta or beta power and alcohol consumption in the patient or matched control groups. Excessive alcohol consumption was an exclusion criterion in our study, but data on alcohol consumption in the matched control group was based on a self-administered questionnaire, which may be vulnerable to underestimation and underreporting

(252). In CSE patients, assessment of alcohol consumption, based on a detailed interview, clinical examination, and previous medical records, was strict and thus more reliable.

Our QEEG findings reflect cognitive dysfunction in the CSE patients and suggest that the frontal cortex is more susceptible than other brain areas to the neurotoxic effects of solvents. This is in line with our brain MRI findings of the most frequent brain atrophy in frontal and parietal areas. Because the findings in QEEG were slight and non-specific, and only 11% of the QEEG recordings were originally interpreted as abnormal, QEEG cannot be recommended in the diagnostics or differential diagnostics of CSE.

6.4 Event-related potentials

Single-task condition

The main result in the auditory ERP study was that – in comparison with laboratory and age-matched controls – CSE patients have decreased auditory P300 amplitudes at Pz. This finding was confirmed in the multimodal ERP study. This result parallels findings in a small CSE patient group very similar to ours in age, exposure, and education (134); although in other studies on CSE patients, P300 amplitude has been normal but latency prolonged (145,146). Findings of decreased amplitudes and prolonged latencies in visual tasks in CSE patients and solvent-exposed workers (113,114) were not corroborated here, perhaps related to differences in study populations or in ERP paradigms. In auditory tasks, the paradigm most commonly used is the standardized oddball paradigm which enables comparisons between ERP studies. In contrast, the visual paradigms applied are much more variable.

Findings of prolonged P300 latency in solvent-exposed workers and CSE patients (69,120,145,146) were in part corroborated in the auditory ERP study. CSE patients had longer P300 latencies than did our laboratory control group but not longer than our age- and education-matched controls. Prolonged P300 latency associates with increasing age (157). The younger age of the laboratory controls does not, however, explain this difference, as age was controlled for in the statistical analyses. Alcohol consumption also associates with prolonged P300 latency

(124,140). The higher alcohol consumption of the age- and education matched control group than that of the patients may thus explain the differences in latency values. In the multimodal ERP study, latencies did not differ between CSE patients and age-matched controls with equal alcohol consumption. Nor did we find any association between P300 amplitude or latency and the amount of reported alcohol consumption.

Differences in ERP results between ours and earlier studies' may be related to differences in study populations. Moreover, whereas most of those studies included solvent-exposed workers without a definite CSE diagnosis, our cases, carefully examined CSE patients meeting strict exclusion criteria, produced more reliable results.

Major depression has been shown to be associated with decreased auditory P300 amplitude and prolonged latency (139). We found no such association in the auditory ERP study, in which we used the DSM-IV diagnostic criterion in retrospective psychiatric re-evaluation of psychiatric medical records. This is in line with a finding of no association in CSE patients between amplitude or latency and Beck Depression Inventory (BDI) scores (145). In the multimodal ERP study, depression was excluded by DEPS. Serotonin reuptake inhibitors, benzodiazepine derivates, and medication with anticholinergic effects are also associated with decreased P300 amplitude (253–255), but we found no such association.

During the follow-up period of on average 14 months (range 10–18) in the auditory ERP study, changes in P300 values at group level were non-significant. One study showed that in solvent-exposed workers, longer time from exposure to test associates with improved P300 latency (256). We found a tendency for improvement in P300 amplitude, although individual changes in P300 amplitude are difficult to interpret due to large intraindividual variability (135). The follow-up results suggest, however, that removal from solvent-exposure work may improve cognitive processing or at least prevent further deterioration of the brain dysfunction in CSE patients, as the ERP results in most of the patients (11 of 19) remained unchanged.

Length of exposure was correlated with P300 latency in one small group of 12 CSE patients (145). In our auditory ERP study, as in the QEEG study, the results did not correlate with exposure indices. This lack of correlation may be related to inaccuracy in assessing exposure,

especially peak exposures. Furthermore, individual susceptibility to the neurotoxic effects of solvents varies, due to several factors such as individual differences in toxicokinetics and metabolism of solvents (28), which in clinical studies are very difficult to control.

Based on the laboratory's reference values, all the individual P300 amplitude values of the CSE patients and the matched controls in the auditory ERP study were classified as normal (i.e., age corrected mean ± 2.5 SD). The latencies were classified as abnormal in 30% of the CSE patients and in 26% of the matched controls. The difference in sensitivity between amplitude and latency may be due to the larger interindividual variability in amplitude values.

Dual-task conditions

The original hypothesis of the multimodal ERP study was that the decrease in amplitude with increasing task demands would be more marked in CSE patients than in controls. This was in part confirmed. The change between the groups in mean auditory P300 amplitudes between AUD, AUD+VIS, and AUD+MEM conditions did not differ. The auditory P300 in the dual-task condition was, however, unrecognizable more frequently in patients than in controls.

P300 amplitude is sensitive to the amount of attentional resources engaged in task performance. Decreased amplitude reflects insufficient allocation of attentional resources during task processing, and decreased brain activity required in the maintenance of working memory (140), i.e., cognitive processes is typically disturbed in CSE (148,149,151–153). In dual-task conditions, meaning concurrent requirements to hold information in working memory or when multiple tasks compete for attention, an increase in the difficulty of the primary task leads to a decrease in the resources available for the secondary task; thus the amplitude from the secondary task decreases (137,257). Stimuli that would normally elicit P300 fail to do so if they are ignored or if attention is directed elsewhere (257). The subjects in our study were not, however, instructed to pay attention either to auditory or visual stimuli. ERP results in the dual-task condition suggest that CSE patients have difficulties in updating information and in dealing effectively with an increase in processing load, due to impaired ability to allocate attentional resources and to shift

attention between two tasks. Similar disturbances can be seen in patients with Parkinson's disease (258).

The duration of the test session in the multimodal ERP study was rather long (about 60 to 90 minutes). Fatigue and a decreased state of arousal during the task performance impair vigilance, i.e., the ability to maintain attention and alertness over prolonged periods of time, which then affects ERP responses. As the dual-task condition with the highest cognitive processing load (AUD+MEM) was performed in the middle of the test session before the AUD+VIS condition, decreased state of arousal does not seem to explain the impaired ERP responses in dual- versus single-task conditions. During the test session, the research technician noted the subjects' alertness. Furthermore, the subjects' performance in Rapid Visual Information Processing (RVP) – an analogy to the Continuous Performance Task (CPT), requiring sustained attention (234) – which was performed immediately after the ERP recording as a part of the neuropsychological test battery, was not impaired, thus reflecting a normal state of arousal.

In dual-task conditions, the amplitude was decreased or the response absent to auditory but not to visual stimuli, which indicates asymmetry in the allocation of attentional resources. This may be explained by the visual dominance theory: when visual and auditory signals are presented simultaneously, subjects generally respond to the visual stimulus and may even be totally unaware of the auditory stimulus (259). Divided attention causes impairment more in auditory than in visual stimulus evaluation (260). One hypothesis states that visual stimuli are less alerting and need to be processed actively, whereas auditory stimuli have an automatic alerting effect (261). More attentional resources are thus allocated to the visual stimulus, which contributes to the higher amplitude values for visual than auditory stimulus, also seen in the multimodal ERP study (260,261).

Task performance

P300 latency is a measure of cognitive processing speed suggested to represent the time required for stimulus evaluation but not for response selection (137,262). Reaction time reflects information processing including stimulus perception, comparison of the current stimulus with the

target in the memory, and selection of the appropriate response, followed by execution of that response (262). Prolonged RT in CSE patients to auditory stimuli in both dual conditions and to visual stimuli in the AUD+VIS condition without any increase in latency may thus reflect deficits in the later phases of information processing, i.e., in selection of the correct response or in the initiation and execution of the response after stimulus identification. When task difficulty increased, the difference in RT between our patients and controls disappeared, which may indicate a ceiling effect and the fact that the ERP paradigm was too difficult. Slower performance speed in the patient group may also account for their inferior, although statistically insignificant, response accuracy, because after 2000 ms any response was considered a miss. Furthermore, presentation of the subsequent stimuli within the response window of the previous stimuli impairs response accuracy.

The association found between prolonged P300 latency in CSE patients and impaired cognitive tests scores, especially in tasks requiring attention (263), was not corroborated here. In the auditory ERP study, our three neuropsychological tests measured various aspects of attention and short-term memory (Digits forward, Digits backward, and Digit symbol substitution). Digit symbol substitution correlated positively with P300 amplitude both in the patient and in the matched control group. This is unsurprising, as P300 amplitude reflects the efficacy of information processing and allocation of attentional resources, and Digit symbol substitution is a complex time-limited task requiring focused, sustained, and shifted attention with demands on visuomotor coordination and psychomotor speed (264, 265).

In the multimodal ERP study, we found no correlation between neuropsychological test results and ERP values. This indicates that the ERP paradigm measures different aspects of cognitive processing than do the neuropsychological tests we applied. Furthermore, surprisingly few statistically significant differences in neuropsychological test results emerged between patients and controls, especially when taking into account the higher mean education of those controls. This may be due to the small size of the study group and the large variation in test results especially in the patient group. The retest effect may also contribute to the results (148), as half the patients were familiar with the cognitive tests. This strengthens, however, the result showing a significant differ-

ence between patients and controls in the performance of Intra-Extra Dimensional Set Shift (IED). IED is analogous to the Wisconsin Card Sorting Test (WCST) and requires shifting and flexibility of attention, attentional set formation maintenance, and visual discrimination (234). PET and fMRI studies have shown that WCST activates the dorsolateral and ventrolateral prefrontal cortex and caudate nucleus, regions important for the set-shifting process and working memory functions (266,267). WCST is sensitive to changes in the fronto-striatal areas and is typically impaired in patients with Parkinson's disease (234). Spatial Working Memory (SWM), which requires the ability to retain spatial information and to manipulate remembered items in working memory, is a sensitive measure of frontal lobe and executive dysfunction. The strategy score in SWM is typically lower in patients with frontal brain dysfunction. The unimpaired performance of CSE patients in SWM and especially high strategy scores may indicate that the cognitive deficits in CSE are related to disturbances not in the frontal brain area but in posterior aspects of frontoparietal continuity. This assumption is supported by our finding of decreased auditory P300 amplitude in CSE patients in Pz but not at Fz. This indicates a posterior disturbance in the neural generators of P300 which involves the widespread cortical network in the prefrontal and parietal cortex, medial temporal complex, and areas of the temporoparietal junction (137,268,269). Interestingly, in aging, accompanied by slowed information processing and a decline in working memory and in attentional abilities, P300 amplitude also decreases in parietal but not in frontal areas (157,165).

6.5 Strengths and limitations of the study

The material of Study I, which was based on comprehensive data sources (clinical patient records at FIOH, FIOH's Register of Industrial Hygiene Measurements, FINJEM, and Statistics Finland), is unique. Furthermore, because the diagnostics of CSE is nationally centralized in the FIOH, the numbers of annually diagnosed cases are inclusive and match the figures of the Finnish Register of Occupational Diseases.

The numbers of exposed workers at differing exposure levels were gathered from FIMJEM. The definition of occupations and agents in

FINJEM limits, however, its use because all workers with the same occupational title are assigned to the same class, irrespective of their actual exposure status or level (235,270). Furthermore, most patients (92%) had been exposed to mixtures of solvents at variable exposure levels. Misclassification of exposure may thus skew the number of exposed workers and lead to incidence-figure unreliability.

Being based on thorough diagnostic procedures at FIOH, including detailed analyses of solvent exposure, multidisciplinary differential diagnostics, and follow-up, the study material is well-characterized, and the CSE diagnosis of all the patients in the five studies is highly reliable. Moreover, the study group of 71 patients in Study II (MRI) and 86 patients in Study IV (auditory ERP) were exceptionally large compared to previous MRI studies on 9 to 32 patients (66,70) and ERP studies on 12 to 20 patients (134,145). The limitation of Study V (multimodal ERP) is the small size of the study group, because of the 26 patients contacted, only 11 were included. This study was, however, basically a pilot study designed to test the multimodal ERP paradigm.

In the MRI study, we used standard images to assess brain atrophy and a validated classification scale to evaluate white matter findings, which has not been done in other CT or MRI studies on solvent-exposed workers or CSE patients. A limitation of the study is, however, lack of any control group. It is especially troublesome if the findings are slight and non-specific, as in our study. As both atrophy and white matter changes increasingly appear with aging, the association of MRI findings and solvent exposure remains indefinite.

ERPs are influenced by several factors (such as circadian rhythm, fatigue, personality, genetic factors) which are difficult to control in clinical studies (140). Because patient characterization in Study IV was based on clinical patient records, a validated questionnaire on depression was unavailable. Depression at the time of ERP recording was assessed by analysis of the clinical psychiatric patient records by a psychiatrist; this makes the diagnosis of major depression reliable. Data on occasional medication, such as sleeping pills, and alcohol consumption during the day preceding ERP recordings was unavailable and thus, their acute effects on CNS and ERP cannot be totally excluded. Smoking, which also affects ERP (142), was disregarded in the analyses. The different methods in assessing alcohol consumption in the patient group (a questionnaire

and an interview) and in the control group (a questionnaire) may have influenced the amount of reported alcohol consumption and thereby the QEEG and ERP results. To study the explanatory effects of confounding etiologies in Study IV, we could have used regression analyses.

Comparison of the QEEG and auditory ERP results between matched controls and laboratory controls revealed significant differences. We chose the age- and education-matched control group of blue-collar workers in order to study purely the solvent effects on EEG and ERP. The laboratory control group was based on the laboratory's reference material on presumably healthy subjects recruited mainly from the staff of FIOH. Data on their alcohol consumption, smoking, medication, mood disorders, and education was unavailable. We included, however, the laboratory control group in the QEEG and ERP studies, because that is the reference material used in clinical practice. The fact that QEEG and ERP results strongly depend on the selection of control material weakens the reliability and sensitivity of these methods.

7. CONCLUSIONS

1. In Finland, the number and incidence of CSE cases during 1995–2007 has declined. CSE affects most probable male spray painters aged over 45 when the duration of occupational solvent exposure mainly to aromatic hydrocarbons exceeds 20 years.

2. CSE is associated with brain atrophy which correlates with duration of exposure. The atrophy and white matter MRI findings in CSE are, however, slight and non-specific, which makes MRI in clinical practice useful mainly in the differential diagnostics of CSE. In other words, if major abnormalities appear in the brain MRI of a patient with suspected CSE, non-solvent etiologies may be implicated.

3. QEEG in CSE patients may reveal slight abnormalities. As the findings are non-specific, QEEG is not recommended for the clinical diagnostics of CSE.

4. In CSE, the P300 amplitude of auditory ERP is decreased. The classical oddball paradigm is, however, insensitive at an individual level and ineffective in clinical practice.

5. The multimodal ERP paradigm seems to provide a more sensitive, although still non-specific, method for individual diagnostics. The results in the multimodal ERP study indicate that CSE patients present with slowed performance speed and deficits in the allocation of attentional resources and in shifting attention, especially when the cognitive load increases. These results also suggest a posterior disturbance in the frontoparietal continuity in CSE.

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ORIGINAL ARTICLES (I–V)

During recent decades, the number of solvent-exposed workers and solvent exposure in many work tasks has diminished. This has led to a decrease in the number of occupational chronic solvent encephalopathy (CSE) patients, but still every year reveals new cases.

This book presents the incidence of CSE in Finland during 1995–2007 and the work tasks and solvent exposure related to CSE. It also presents the findings in brain magnetic resonance imaging, electroencephalography, and event-related potentials and discusses their diagnostic value in CSE.

Orders:
Finnish Institute of Occupational Health
Topeliuksenkatu 41 a A
FI-00250 Helsinki
Finland

Fax +358-9 477 5071
E-mail kirjakauppa@ttl.fi
www.ttl.fi/bookstore

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