KUOPION YLIOPISTON JULKAISUJA D. LÄÄKETIEDE 316
KUOPIO UNIVERSITY PUBLICATIONS D. MEDICAL SCIENCES 316

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Information Processing in Acute Psychosis

Doctoral dissertation

To be presented by permission of the Faculty of Medicine of the University of Kuopio for public examination in Auditorium L3, University of Kuopio, on Friday 14th November 2003, at 12 noon

Department of Psychiatry
University of Kuopio and
Kuopio University Hospital

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ISBN 951-781-356-2
ISSN 1235-0303

Kopijyvä
Kuopio 2003
Finland

Valkonen-Korhonen, Minna. Information Processing in Acute Psychosis. Kuopio University Publications D. Medical Sciences 316. 2003. 146 p.
ISBN 951-781-356-2
ISSN 1235-0303

Abstract

Psychosis is defined by grossly impaired reality testing. Psychotic persons incorrectly evaluate their perceptions and thoughts and make incorrect inferences about external reality, even in the face of contrary evidence. The aim of the current project was to study psychosis as a psychophysiological state by recording an eletrophysiological test-battery comprising several levels of physiological reactions to external stimuli, and by comparing the findings from 25 drug-naïve acutely psychotic first-episode patients with 21 healthy volunteers. Psychotic patients showed a lack of time-locked sympathetic skin reactions and decreased short-term heart rate variability, implicating profound disturbances in the autonomic nervous system and adaptability. Patients displayed an enhanced auditory N1 component emphasized in frontal recordings reflecting changes in stimulus detection. They also showed decreased amplitudes of attention-dependent components of the auditory "oddball" paradigm (N2b, P3a and P3b). Concerning visual modality, event-related potentials evoked by human face stimuli were examined. The early component reflecting visual detection did not differ between the groups. However, a significant hypernegativity was associated with two stimulus content related components (N145 and P230). Acute early psychosis seems to enhance automatic cerebral responses, decrease conscious later components and disturb the reactivity and timing of autonomic nervous system responses. These findings are discussed as markers of general disorganisation in psychosis with an attempt to incorporate them into unifying theoretical models of psychotic illnesses.

National Library of Medical Classification: WM 200

Medical Subject Headings: psychotic disorders; acute disease; event-related

potentials; schizophrenia; electroencephalography; heart rate; face;

galvanic skin response

For the Great Lonely in Saana Fjeld

Acknowledgements

The fieldwork of this study was carried out in the Department of Clinical Neurophysiology at Kuopio University Hospital, during the years 1997-2000. I am sincerely thankful to Professor Juhani Partanen for this opportunity as well as his help and support during all these years.

The analysis work was performed in the Department of Psychiatry at Kuopio University in collaboration with the Department of Clinical Neurophysiology and the Department of Applied Physics at Kuopio University during the years 1998-2003.

I owe my warmest and deepest gratitude to my supervisor, Professor Johannes Lehtonen from the Department of Psychiatry. He has introduced me the captivating world of interdisciplinary psychiatric research and tutored me during all these years through several conceptual and theoretical pitfalls. His admirable open-mindedness guaranteed a freedom of developing own scientific thinking, yet he was willing to share his knowledge and discuss. He has also enabled me to do this work in good conditions.

I am no less indebted to my supervisor Docent Jari Karhu from the Department of Clinical Neurophysiology for his enthusiasm and inspiring ideas, which were especially crucial during the first difficult years of the planning phase of the study, and concerning many problems in analysis and writing. He first suggested me the idea of a psychophysiological thesis.

This study was reviewed by Professor Matti Huttunen from Helsinki and Professor Robert Oades form Essen. I am very grateful for their efficient work and encouraging comments and valuable review.

I wish to express most sincere thanks to Docent Ina M. Tarkka from the Brain and Rehabilitation Center Neuron, for her supporting comments, constructive criticism, and for bringing hope to each disasterous turn of the project. Her self-sacrificing help and teaching from the beginning up until last weeks' finishing was impressive.

Maija Purhonen, MD, a close companion, is probably the only one who knows where I have been, because she was there with me, and she has my deepest gratitude. I thank her for commenting all my manuscripts and forming a duo in resolving technical problems. Her sensible advice and supportive point-of-views, at the moments of exhaustion and disappointments, recurrently rescued me continue with the study. And those many tears of laughter, of course!

I wish to thank Ari Pääkkönen, PhD, for his help in building up the recording set, with the recordings and his valuable comments on analysis details and manuscripts. I am also thankful to the whole physicist team at the Department of Clinical Neurophysiology, they have listened to my problems so many times and teached me how to use a computer, Windows and NeuroScan from the very first beginning: Mervi Könönen, Heidi Yppärilä, Anu Koistinen (Holm), Jukka Kinnunen and others. I also thank Perttu Sipilä and Jan Kremlacek for their help in Curry analysis.

The fact that we succeeded in this study was an achievement thanks to the high professional quality of assisting personnel and the amazing cooperativeness of the patients. I am deeply grateful to all the individuals who were willing to participate in the study even if they had difficult times in their lives.

I wish to thank warmly Outi Leppälinna and all personnel at the Department of the Clinical Neurophysiology for their experienced actions during the preparation of the recordings and for great adaptability in scheduling the recordings enabiling us to get acute phase data.

I am very grateful to Professor Pasi Karjalainen for rewarding collaboration at the Department of Applied physics, and for his valuable comments and ideas for the HRV and SSR analysis. I thank warmly Mika Tarvainen and Perttu Ranta-Aho for our collaboration during the preparation of SSR and HRV analysis, and Juha-Pekka Niskanen for recent undertakings.

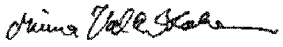
I warmly thank Pirjo Halonen for her help in statistical analysis problems and Roy Siddahl for English proof-reading the thesis. I thank Hanna Seppänen and Riikka Byckling for proof reading the abbreviations and references.

I wish to thank all my researcher colleagues, juniors and seniors, for inspiring discussions during all these years many of which took place in the TUKE coffee room: Kaisa Haatainen for first aid and neighbourliness, Ulla Hintikka, Kirsi Honkalampi, Heli Koivumaa-Honkanen, Aija Koivu, Suvi Andersin and others. I am fulfilled with happy appreciation of all my friends and relatives near and far for not leaving me alone when I was tired and passive myself. My special honor goes to Liisa I. Kerttula, PhD, my dear friend and the chair of the Pummin Suunta organization, which I also thank for most gratifying support, via diverse physical and mental activities. I thank my father for bringing science in my life and my mother for always taking care of me and my family. I thank Mika for being the brother. I thank Miitu and Jirli for putting this study into right perspective in my mind, both by being themselves and by their ideas of a perfect book, and I am sorry this work took so long.

My most cordial gratitude belongs to my beloved husband, Ilkka, for his help and support from technical help in computer applications and proof-reading the references up to sharing his life with me. He always brought off maintaining our puzzle entire even if I kept loosing pieces.

This study was financially supported by Kuopio University Hospital, the Academy of Finland, and the Signe and Ane Gyllenberg Foundation.

Kuopio, October 2003



Minna Valkonen-Korhonen

Abbreviations

ANS	Autonomic nervous system
AR	Autoregressive modeling
BESA	Brain electrical source analysis
BSEP	Brain stem evoked potentials
CCTCC	Cortico-cerebellar-thalamic-cortical-circuitry
CNS	Central nervous system
CNV	Contingent negative variation
CPT	Continuous performance test
CT	Computerized tomography
DPFCx	Dorsolateral prefrontal cortex
DR	Defence reflex
DSM	Diagnostic and statistical manual of mental disorders, version numbers III(R) and IV
ECG	Electrocardiogram
EDA	Electrodermal activity
EEG	Electroencephalogram
EP	Evoked potential
ERP	Event-related potential
FFT	Fast Fourier transformation
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GFP	Global field power
GLM	General linear model
GSR	Galvanic skin response
HF	High frequency

HR	Heart rate
HRV	Heart rate variability
ICD	International classification of diseases
IPAP	Information processing in acute psychosis
ISI	Interstimulus interval
ITI	Intertrain interval
LDAEP	Loudness dependence of auditory evoked potential
LF	Low frequency
MAEP	Middle latency auditory evoked potential
MEG	Magnetoencephalogram
MMN	Mismatch negativity
MNE	Minimum norm estimate
MRI	Magnetic resonance imaging
NMDA	N-methyl-D-aspartate
OR	Orienting response
PANSS	Positive and negative symptom symtom scale for schizophrenia
PASP	Peripheral autonomic surface potential
PCA	Principal component analysis
PET	Positron emission tomography
PGR	Psychogalvanic reflex
PPI	Prepulse inhibition
PSD	Power spectral density
QEEG	Quantitative electroencephalogram
RMSSD	The square root of the mean squared differences of successive R-R intervals
R(-)R	Consequtive R peaks in electrocardiogram

RSA	Respiratory sinus arrhythmia
SCR	Skin conductance response
SPECT	Single photon emission tomography
SSR	Sympathetic skin response
VEP	Visual evoked potential
VIP	Vasoactive intestinal polypeptide
VLF	Very low frequency
VPP	Vertex positive scalp potential
WCST	Wisconsin Card Sorting Test

List of original publications

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I Valkonen-Korhonen M, Karjalainen P, Lehtonen J, Koistinen A, Partanen J, and Karhu J: Loss of time-organized sympathetic skin responses in acute psychosis. Journal of Nervous and Mental Disease 189(8):552-556, 2001.

II Valkonen-Korhonen M, Tarvainen, M, Ranta-aho P, Karjalainen P, Partanen J, Karhu J, and Lehtonen J: Heart rate variability in acute psychosis. Psychophysiology 40(5):716-726, 2003.

III Valkonen-Korhonen M, Könönen M, Yppärilä H, Sipilä P, Lehtonen J, Partanen J, Tarkka IM, and Karhu J: Cerebral signs of altered adaptability in females with acute psychosis. Schizophrenia Research 55(3):291-301, 2002.

IV Valkonen-Korhonen M, Purhonen M, Tarkka IM, Partanen J, Karhu J, and Lehtonen J: Altered auditory processing in acutely psychotic never-medicated first-episode patients. Brain Research: Cognitive Brain Research 17(3): 747-758.

V Valkonen-Korhonen M, Tarkka IM, Pääkkönen A, Kremlacek J, Lehtonen J, Partanen J, and Karhu J. Electrical brain responses evoked by human faces in acute psychosis. Submitted.

Contents

1. Introduction

In the 1990s the manifestation of biological reductionism culminated in the "Decade of the Brain" following the spectacular advances of neurobiology, neurochemistry and neurophysiology in the 1970s and 1980s. Despite abundant research, the etiology, pathogenesis, and even pathophysiology of psychotic illnesses still remain largely unknown, leaving them as syndromes at the level of diagnostic specificity. Moreover, the heterogeneity of patient groups within the symptom clusters raises a need to improve ways of categorizing the psychic phenomena involved. This is further stressed by recent evidence of the importance of early therapeutic intervention in psychotic illnesses in order to improve the overall prognosis and prevent long term complications. New, simple and cost-effective methodologies suitable for screening people at risk and testing pro-dromal patients are urgently being sought. New tests are sorely needed to direct expensive and invasive methods effectively, to obtain more homogenous patient samples with more informative results, and above all, to enable the clinical recognition of those patients requiring early therapeutic intervention.

A sign is an objective manifestation of a pathological condition (Pull 2000). Psychosis encompasses several severe alterations in thoughts, emotions and behaviour, yet being a sign of severe mental dysfunction in itself. Psychosis is also a condition wherein objective clinical observation of the person gives the most accurate information of the state, since the lack of insight usually restricts the anamnesis obtained by the interview. Thus, in acute psychosis signs, as objective manifestations, are emphasized in favour of symptoms, which may be confusing for the interviewer, although it is not usually difficult to distinguish between psychotic and non-psychotic subjects in the acute state. Better comprehension of the underlying psychophysiology may help the observation of the subject and create a better understanding of the patient's needs when making diagnostic and therapeutic decisions.

Based on the aforementioned scientific and clinical background, the current project was established in 1996 in an effort to outline a multilevel psychophysiological profile

of the acute psychotic state. The project was performed in collaboration with the Departments of Psychiatry and Clinical Neurophysiology at Kuopio University Hospital and Applied Physics at Kuopio University. Psychophysiological measures involve both physically and psychologically noninvasive methods with a relatively long history of recording techniques and rapidly advancing computerized analytical techniques for signal-processing. Consequently, the project provided an opportunity to use an interdisciplinary approach and cooperation in an effort to identify new aspects of psychotic illnesses, thereby representing one local gesture in favour of the general scientific move towards a more holistic approach in psychiatric research.

2. Background – review of the literature

2.1. Psychosis – definition, diagnostics and clinical picture

The term "psychotic" has recently been used widely with multiple meanings other than its biological definition (Kaplan & Sadock 1996). As a consequence, diagnostic categories such as schizophrenia, manic-depressive disorder, affective psychoses and delusional disorder have, in many cases, replaced "psychosis" in clinical use. The heterogeneity of symptoms and signs, even within a particular diagnosis group, has raised questions of disease boundaries (Kendler 1999) and the structure of psychosis (Crow 1998, Kendler et al. 1998, Kendler & Walsh 1998), leading to the reformulation of diagnoses (Tsuang et al. 2000a). The current trend is in a more dimensional and functional direction (McIntosh et al. 2001, Verhoeven & Tuinier 2001), towards a "unitary psychosis" theory. In the following chapter, the concept of psychosis as well as the underlying diagnostic variation is outlined.

2.1.1. Definition

The traditional meaning of the term "psychotic" emphasizes the loss of reality-testing and impairment of mental functioning manifested by delusions, hallucinations, confusion, and impaired memory (Sadock & Kaplan 1996). The term is also commonly used in clinical practice to mean severe impairment in social and personal functioning characterized by social withdrawal and an inability to cope with daily activities. In the psychodynamic approach, psychosis means a degree of severe ego regression (Sadock & Kaplan 1996). According to the glossary of the American Psychiatric Association, the term "psychotic" means grossly impaired in reality testing. The term may be used to describe the behaviour of a person or a mental disorder that includes episodes of grossly impaired reality testing. With gross impairment in reality testing, persons incorrectly

evaluate the accuracy of their perceptions and thoughts and make incorrect inferences about external reality, even in the face of contrary evidence. Minor distortions of reality that involve matters of relative judgment are not to be considered as psychotic signs. However, a person's behaviour may sometimes be so severely disorganized that it can be considered a disturbance of reality-testing (Sadock & Kaplan 1996).

2.1.2. Historical view on the categorization of psychotic illnesses

The first decripstions of schizophrenia symptoms date back 3500 years, but by the 19th century psychotic disorders were viewed generally *e.g.* as either madness or insanity. The research of syphilitic insanity lead Emil Kraepelin identify also two other patterns of insanity, manic-depressive psychosis and dementia praecox (*Dementia Praecox and paraphrenia*, published 1919), his work is regarded as the father of the categorization and conceptual framework of psychotic disorders (Kraepelin 1919). Eugen Bleuler continued his work and first introduced the term schizophrenia (Bleuler 1950), and differentiated the primary symptoms of schizophrenia (thought disorder, psychotic ambivalence and autistic withdrawal) from secondary symptoms (hallucinations, delusions, and catatonic modes of behaviour).

However, the first widely used classification of psychotic symptom domains into positive and negative subdivisions started to grow even earlier, when Hughlings Jackson paid attention to the similarities in psychoses and epilepsy as early as the 1850s (Trimble 1996). His main theories dealt with the evolution of nervous functions, the hierarchy of functions, the negative (anhedonia, avolition, powerty of speech and affective blunting) and positive (hallucinations, delusions, disorganized speech and behavior, and catatonic symptoms) symptoms of dissolution and the distinction between local and uniform dissolution (Trimble 1996, Suvisaari 1999). In many ways, his theories may provide historical routes to the current project. Suvisaari (1999) has presented a compact and thorough literature review of the evolution of the diagnostic concept of schizophrenia from Kraepelin to DSMIV (Diagnostic and Statistical Manual of Mental Disorders, version IV), wherein the whole spectrum of psychotic illnesses is

presented.

The variable results of positive-negative research in schizophrenia underscore the importance of well-characterized, standardized measurement techniques. The initial standardization of the Positive and Negative Symptom Scale (PANSS) for typological and dimensional assessment was published in the 1980s (Kay et al. 1987). Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides a balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. Positive, negative and disorganized symptoms have been found in several psychotic illnesses (Rotakonda et al. 1998). The PANSS represents the most diversified and valid rating scale for psychotic symptoms (See Table 1), even if the heterogeneity of diagnostics has led to a growing interest in defining specific groups of symptoms or domains of psychopathology that might be used to identify clinically, pathophysiologically, and etiologically more homogenous patient groups (Suvisaari 1999).

Positive symptoms (P1-7)	**Global Psychopathology (G1-16)**
Delusions	Somatic concern (Health concern)
Conceptual disorganization	Anxiety
Hallucinatory behavior	Guilt
Excitement	Tension
Grandiosity	Mannerisms and posturing
Suspiciousness	Depression
Hostility	Motor retardation
	Uncooperative behavior
Negative symptoms (N1-7)	Unusual thought content
Blunted affect	Disorientation
Emotional withdrawal	Poor attention
Poor rapport	Lack of judgment and insight
Passive-apathetic social withdrawal	Avolition
Difficulty in abstract thinking	Poor impulse control
Poverty of thought and spontaneous activity	Introversy (Self-centeredness)
Stereotyped thinking/behavior	Active social avoidance

Table 1. Positive and negative symptoms and the symptoms of global psychopathology ranked in Positive and Negative Symptom Scale (PANSS).

2.1.3. Psychotic signs and symptoms

Psychosis encompasses both perception and thought. The impaired perceptions involve illusions and hallucinations, which may concern any sensory modality (sensory, auditory, visual and others). Body image distortions can also be comprised as an example of psychotic perceptual problems (Yager & Gitlin 1995). In perceptual domain the loss of reality-testing can be seen as an inability to unambiguously differentiate between internal experiences and perceptions of the external world, or the observations of the external world may be distorted (Alanen 2000).

Thinking disturbance in psychosis may reflect different types/categories of thinking process (in psychosis, so-called primary process thinking substitutes normal thinking), thinking rate (slowed or retarded thought, thought blocking, thought withdrawal, flight of ideas), continuity of thinking (tangentiality, derailment, loose associations, word salad, clang association, perseveration, stereotypy and crowding of thought), thought control (delusional thought passivity, thought insertion, thought broadcasting, obsessional thinking), and complexity of thinking. The thought content may be disturbed by delusions of different types. Disturbances of judgment are common in psychotic patients and most frequently concern their own state, symptoms and need for treatment (Yager & Gitlin 1995).

Consciousness disorders involve awareness of the self and the environment, and the matter can be considered from both quantitative and qualitative points of view. Levels of consciousness (alertness, awareness and attentiveness) can be increased or decreased in psychosis: a mild increase in consciousness may be seen in hyperesthesia of the prodromal phase of psychosis, a more severe increase in attention fragments, unpleasant hyperesthesia and alertness transformation into paranoia. Mild decreases in the level of consciousness are often seen in psychotic states, *i.e.* shattered consciousness is marked by decreased awareness of sensory cues and reduced attentiveness to the environment and to the self. Confusion and distractibility are also common findings. Other types of psychotic thought disturbance involve disorders of will, and diverse memory impairments (registration/encoding, retention, recall). Mood swings, anxiety,

aggression, and motor disturbances are less specific signs of psychosis. Disturbance of the self, however, takes us back to the original definition of psychosis as the disturbance of boundaries. (Yager & Gitlin 1995)

2.1.4. Etiological and pathophysiological issues

While no specific etiological or pathophysiological factors for psychotic illnesses have yet been reported, several vulnerabilities and stressors seem to exist. Genetic factors may contribute to different levels of psychotic organization of the mind: an inherited defect of dopamine regulation, exaggerated psychophysiological arousal responses to stimuli, psychologically blunted responses, and so on (Yager & Gitlin 1995). Intrauterine factors include neuroimmunovirology hypotheses and birth and pregnancy complication hypotheses. Constitutional factors (temperament) may also influence the appearance of psychosis. Physiological stressors, as well as stressful life-events, have been shown to enhance the risk of a psychotic episode. There are also theories of the involvement of environmental factors in the risk of psychotic illness.

2.2. Autonomic nervous system in psychotic illnesses

In the clinical picture of an acute psychotic episode, autonomic hyperarousal is often evident in the form of dilated pupils, moist palms, moderate tachycardia, and elevated systolic blood pressure, which can be observed even if the patient shows no overt signs of emotional excitation (Kaplan & Sadock 1996).

The essential function of the autonomic nervous system (ANS) is to maintain the constancy of the internal environment, *i.e.* to maintain homeostasis. The ANS has three major divisions: sympathetic, parasympathetic, and enteric, the former two of which have the primary role in regulating the internal processes. The sympathetic system governs the "fight and flight" reaction, and the parasympathetic division is responsible of the "rest and digest" functions. (Dodd & Role 1991) Despite their contrasting

functions, these two control mechanisms share similar mechanisms and neurotransmitters and the controlling mechanisms show advanced interaction. This means that a particular transmitter may engage in both sympathetic and parasympathetic functions, and furthermore, it may have both excitatory and/or inhibitory effects.

The methods used to record ANS function are essentially old-fashioned, which may also give methodological advantages: the tools are simple to use, of low cost, psychologically and physiologically noninvasive and suitable for studying the effects of single stimuli (Venables 1991). The disadvantage is that these measures provide only indirect evidence of higher processes such as brain activity. Moreover, they involve systems with multiple functions. However, ANS recordings provide a "window to the brain" as current indices of the subject's state, either as a tonic measure of his/her ongoing activity or as a phasic measure of his/her response to an individual stimulus. They cannot be considered as an index of any particular part or function of central nervous system (CNS) (Venables 1991).

The hypothalamus helps to regulate the autonomic nervous system and is involved in emotional behaviour and drives as well as in motivated behaviour together with the limbic structures, which are also closely linked with the hypothalamus. The system interacts with neocortical structures in regulating emotions. Another important regulatory task of the ANS involves arousal – maintaining a general state of awareness (Kupfermann 1991). Because of all these connections and qualities, ANS measures are still of great importance in modern psychiatric and psychophysiological research.

2.2.1. Sympathetic skin response

Electrodermal activity (EDA) has been one of the most widely used instruments in the history of psychophysiology. EDA applications range from basic research examining attention, information processing, and emotion to more applied clinical research examining correlates of normal and pathological behaviour and risk-factors. (Dawson et al. 2000)

The terminology applied to electrodermal activity has varied in previous studies. It has often been referred to as the galvanic skin response (GSR) or psychogalvanic reflex (PGR). In clinical neurophysiological literature, the response is known as the peripheral autonomic surface potential (PASP), skin potential response, or more commonly the sympathetic skin response (SSR; (Gutrecht 1994)). More recently these measures have been partly replaced by the skin conductance response (SCR), which is less sensitive to hydration effects of the skin and thus more reliable when amplitudes are of interest (Fowles et al. 1981). On the other hand, the SSR is more sensitive and thus more suitable for evaluating response pattern characteristics and responder types. However, both give largely similar information about ANS reactivity.

Early investigators used a galvanometer to measure the increases in skin conductance that occurred when sensory stimuli were introduced (Andreassi 2000). Two techniques can be used in EDA recordings, both first developed in 19th century. Fere's procedure involved a passing of a small current between the two electrodes placed on the skin (approximates to present-day skin conductance measures, SC), and Tarchanoff's method obtained similar deflections in galvanometer without using any externally applied currents (Andreassi 2000) (today's skin potential, SP).

The physiological bases for these responses are not fully understood, but changes in sweat gland activity have been strongly implicated. Since the sweat glands are most numerous in the palms of the hands, the electrodes are usually fixed on the hypothenar eminence or medial palmar phalances of the hand. For SC recordings a bipolar, and SP recordings a unipolar placement is recommended (Andreassi 2000). Nonpolarizing electrodes should be used in both measures with commercial jellies and pastes. The skin potentials can be measured by a sensitive DC amplifier, and they are analyzed rather unprocessed.

From SC data several analyses can be made: the conductance level, the number of conductance changes, the amplitude and latency of SC reaction and the half-time recovery. The number SP reactions can be calculated within a period of time, or the positive and negative amplitudes and corresponding latencies may be measured, and

peak-to-peak amplitudes can be used to assess the magnitude of the response.

Electrodermal activity is distinct from other autonomic measures in that it is mediated by sympathetic processes rather than by a combination of sympathetic/parasympathetic contribution (Dawson et al. 1994). The brain regions that have been associated with modulation of the SCR include the ventromedial frontal region, anterior cingulate gyrus, and right inferior parietal region (Tranel & Damasio 1994). More recently, activation of the right orbitofrontal cortex, anterior insula, and fusiform gyrus as well as left lingual cortex and cerebellum have been associated with spontaneous fluctuations of the SCR shown with functional magnetic resonance imaging (fMRI) (Critchley et al. 2000). The SSR is also typically elicited by a novel stimulus, which activates a distributed cortical network involving prefrontal and posterior association cortices and the hippocampus (Knight & Nakada 1998).

Tonic electrodermal measures can provide an index of general sympathetic arousal and activation, whereas phasic changes in skin conductance or potential responses have been used to index the allocation of attention and orienting. Both tonic electrodermal hyperactivity and phasic electrodermal hyporeactivity have been identified in schizophrenia (Öhman 1981, Dawson et al. 1992). Responses have also revealed both state-sensitive episode indicators and trait-like vulnerability characters, which fluctuate in different clinical conditions. Dawson et al. (1992) have proposed a "vulnerability stress model" in which sympathetic arousal plays an active mediating role in the psychotic decompensation process. This model also provides an attempt to determine the different responder groups found in previous studies and identify the distinct characteristics of the behaviour of the responses in the responders and non-responders in an effort to clarify the state-trait relations of the ANS deficits during the disease process.

2.2.2. Heart rate variability

Heart rate variability (HRV) describes the variation between consecutive heart-beats and is a reliable quantitative marker of autonomic nervous activity (1996a, 1996b). HRV reflects individual differences in adrenergic reactivity to daily stressors. It varies as a function of age-related, genetic, dietary, task, metabolic, and social factors. Cardiac reactivity also predicts endocrine and immunologic responses to laboratory stressors. (Cacioppo et al. 1994) Furthermore, it can be used as a tool for assessing the integrity of the autonomic nervous system, the interaction between psychological states and autonomic control, and the pathophysiology of diseases that involve autonomic function. (Berntson et al. 1997)

HRV quantification can be approached by using global descriptive statistics to characterise the distribution of heart periods. Nevertheless, although these time domain measures are sensitive to the distribution characteristics of the data, they do not support quantitative assessment. Another means for quantifying HRV is to extract the frequency components of variance related to functions or physiological processes.

Power spectral density (PSD) analysis of RR intervals (*i.e.* consecutive heart beats, R peaks) provides a highly reproducible tool to assess the functional balance between parasympathetic and sympathetic domains of autonomic nervous system activity. Spectral analysis produces a decomposition of the total variation of a data series into its frequency components, the most commonly used techniques being Fast Fourier transformation (FFT) and autoregressive modeling (AR). FFT includes all data and is considered more descriptive, whereas AR excludes noise resulting in a more statistical approach. Despite the differences in advantages and disadvantages of the two methods, in practice they usually produce in equivalent results. (Berntson et al. 1997)

Variations in high frequency (HF) HRV appear to provide a selective index of vagal control of the heart, whereas low frequency (LF) variability is a product of both sympathetic and parasympathetic influences of the heart (Berntson et al. 1997). HF and LF derive from at least partly distinct mechanisms.

In healthy young individuals at rest, the most conspicuous of the periodic components of HRV is respiratory frequency (respiratory sinus arrhythmia, RSA), considered to range from about 0.15 Hz to 0.4 Hz. This may provide an index of vagal activity. RR interval oscillations at low frequencies (LF), about 0.05-0.15 Hz, have been suggested to reflect mainly sympathetic outflow, but the majority of researchers consider them to be of both sympathetic and vagal origin. Very low frequencies (VLF) and ultra low frequencies include circadian rhythms, changes in activity, posture, breathing, autonomic outflow and the state of arousal, and a range of behavioral variables, thermoregulatory cycles and fluctuations in plasma renin activity. However, the origins and mechanisms remain unclear. (Berntson et al. 1997)

The timing of dynamic and steady-state effects also seem to differ between vagal and sympathetic control of the HR: the parasympathetic nervous system is able to modulate the HR at all frequencies between 0-0.5 Hz, but the sympathetic system modulates the HR only below 0.1 Hz (Berntson et al. 1997).

Baroreceptor reflexes contribute to RSA, which is fluctuated by both sympathetic and parasympathetic activities on a breath-by-breath basis (Berntson, Bigger et al. 1997). Although RSA can be substantially affected by breathing, RR intervals may remain constant over a wide range of breathing frequencies. (Berntson et al. 1997) The magnitude of RSA provides a suggestive indication of basal levels of vagal cardiac nerve traffic (Berntson et al. 1997).

The heart rate is increased either by reducing parasympathetic activity or by increasing sympathetic tone. These two functionally antagonistic sources of innervation provide a dual control system. The autonomic branches are not always reciprocally controlled and can vary independently or demonstrate co-activation or co-inhibition. Electrodermal measures have the advantage of being an index of only one branch of the ANS, but measures of cardiac activity provide complementary information about the sympathovagal balance. Furthermore, unlike EDA, HRV is independent of conditions such as electrolyte concentration at the recording site or temperature (Venables 1991).

Schizophrenia is associated with prominent sympathetic hyperarousal (Joseph 1989),

as has been demonstrated in galvanic skin responses (Dawson et al. 1992, Dawson et al. 1994) and heart rate variability (Gruzelier 1975, Malaspina et al. 1997). Antipsychotic medication alters autonomic nervous functions. Despite abundant research there have been few psychophysiological studies on entirely drug-naïve acutely psychotic patients. Consequently, our knowledge of changes in the autonomic nervous system in an acute psychotic state that are not related to drug-effects or the chronicity of the state is limited.

2.3. Electroencephalogram (EEG)

Mental processes are nearly instantaneous (*i.e.* they happen within hundreds of milliseconds), and high temporal resolution of any recording is necessary to detect the phenomena. Neuronal activity in the brain can be studied directly by recording spontaneous electrical activity from the surface of the scalp (electroencephalogram, EEG) in the form of electrical field potentials. Local field potentials and multi-unit activity reflect the current flow caused by post synaptic potentials in neuronal populations, the majority of which originate in the large pyramidal cell layers of cerebral cortical layers (Coppola & Hyde 1995). Changes in the interaction among neurons and within the neuron reflect the electrical activity of not only pathological conditions in the brain but also important correlates of behavior and the normal brain (Coppola & Hyde 1995).

The main advantage of the EEG is that it provides a temporal resolution in the millisecond range. However, the voltage distribution at the scalp is modified by the intervening tissue layers and the complex geometry of the cortical folding (Coppola & Hyde 1995). The activation at the cellular level represents a current source, the simplest representation of which is a dipole. The voltage distribution at a distance from a dipole can be predicted (forward problem), however, the location of a current source recorded from the distance can be calculated using the inverse problem solutions and the given voltage pattern (Coppola & Hyde 1995). In general, the complexities of the cortical

convolutions, the number of generators, synchronization, and the location relative to the scalp overwhelm the purely mathematical problem. All mathematical solutions to resolve the problem appear defective. Thus, the poor spatial resolution of especially the traditional EEG technology remains the main disadvantage of EEG methods, although new techniques are being developed in order to provide new more accurate approximations. One solution might be to combine the information gained with imaging techniques apart from electrophysiological ones (fMRI and/or PET). Moreover, the mathematical and statistical models used to resolve the inverse problem (Koles 1998) are improving, although there is no unique solution to the inverse problem (Gevins et al. 1999, Davidson et al. 2000).

The thalamic nuclei and nucleus reticularis in particular are important pace-makers of the EEG (Davidson et al. 2000). There is evidence of individual cells that can produce rhythmic activity even in the absence of synaptic input. Populations of such cells are able to sustain oscillatory behaviour and influence other neuron populations (Nunez 1981, Coppola & Hyde 1995, Davidson et al. 2000). The oscillatory activity forms the basis for processing and transmission of information in the brain. Several examples of oscillation dynamics and reactivity have recently been demonstrated (Lopez da Silva et al. 1997, Tesche & Karhu 2000a, Basar et al. 2001, Herrmann & Knight 2001, Keil et al. 2001). Understanding the mechanisms behind the dynamic activity of the neocortex and the oscillatory behaviour involves models of networks and the dynamics of the individual elements (Coppola & Hyde 1995). Despite problems in the spatial resolution of EEG methods, the millisecond temporal resolution enables the study of the detailed dynamics of these regional interactions, which can further be combined with, for example, structural information from magnetic resonance imaging (MRI).

The clinical assessment of the EEG, however, is based on systematic visual analysis. The EEG record is evaluated in terms of the following descriptors: amplitude, frequency, waveform, topography, reactivity and symmetry. Studies of the EEG and evoked potential (EP) have been greatly extended with recent advances in computer and graphic display technology. A number of different terms have been applied to the various newly developed methods, including quantitative EEG techniques (QEEG),

computerized EEG mapping, and topographic brain mapping (Nuwer 1997, Hoffman et al. 1999, Wackermann 1999). Methods of presenting EEG in a graphical form, which resembles scalp or brain topography, are popular in these days, and care should be taken not to take such displays too literally in terms of the localization of actual brain activity.

2.3.1. Quantitative electroencephalogram

Spectral analysis is a computer-based method for analyzing the EEG frequency spectrum over time (Pivik et al. 1993). It allows the determination of the relative predominance of power of any frequency band. Background EEG frequency data is transformed into concise parameters by utilizing a method called the Fast Fourier transformation, similarly to HRV analysis (*cf.* page 29).

The correlation between the spectra of contralateral or adjacent leads provides a measure of EEG coherence. A subtle neuropathological process may be detected only by observing a change in the coherence or relative EEG power of specific frequency bands (Knyazeva & Innocenti 2001). In addition, measurements of coherence (Nunez et al. 1997) or the correlation or covariance of EEG time-series from different electrode sites helps to generate hypotheses about the functional networks in the dynamic brain (Gevins et al. 1999).

2.3.2. Conventional and quantitative EEG findings in psychotic illnesses

Abnormal qualitative EEGs have been described in 20% to 60% (80%) of schizophrenic patients (Neylan et al. 1992, Hughes & John 1999), although controlled studies have resulted in lower rates. There are no specific EEG findings for schizophrenia, while most studies show that schizophrenic patients have more abnormalities than control subjects. One of the more specific findings is a relatively low mean alpha frequency, deficient alpha power and diminished alpha reactivity in schizophrenia and bipolar

disorder, but some patients show fast alpha activity (James & Barry 1980, Shagass et al. 1984, Hughes & John 1999). Numerous studies have reported increased beta activity in schizophrenia and bipolar disorder (James & Barry 1980, Hughes & John 1999). Neuroleptics typically have increased alpha activity and decreased beta activity, suggesting normalization of the EEG by medication (Coppola & Hyde 1995). Increased delta and theta powers have also been reported in relation to schizophrenia (James & Barry 1980, Shagass et al. 1984, Hughes & John 1999), even in connection with acute hallucinations (Whitton et al. 1978, Stevens & Livermore 1982, Ishii et al. 2000). Often this is a result of medication effects. Catatonic patients often even present paroxysmal activity (Hughes & John 1999).

The evident inconsistencies in (Q)EEG findings in psychotic illnesses may arise from the coexistence of several subtypes with different QEEG profiles within the population of psychotic patients. John et al. (1994) have reported five subtypes of schizophrenia based on their QEEG profiles, three of which existed in never-medicated patients. Laterality changes in the EEG associated with psychotic illnesses remain controversial, too, but increased delta activity in the left anterior temporal area has been reported to discriminate schizophrenic patients from normal controls. Increased interhemispheric coherence in anterior regions has also been found to be repeatedly associated with schizophrenia, which may contribute to distinguishing bipolar disorder from schizophrenic psychoses (Hughes & John 1999). The principal clinical use of the EEG in psychotic illnesses, however, involves the screening of gross neuropathology or seizure disorder, even though an abnormal EEG may predict drug resistance to neuroleptic medications (Westphal et al. 1990, Joutsiniemi et al. 2001).

2.4. Evoked potentials – event-related potentials and underlying processes

Evoked potentials (EPs) reflect the specific activation of neurons as opposed to the spontaneous activity recorded by an EEG. EPs can be elicited by sensory stimulation

(extrinsic) or arise from cognitive or affective factors (intrinsic). Certain pathways and neural generators are associated with specific EP components (*e.g.* brainstem potentials, BSEPs) (Coppola & Hyde 1995).

Sensory EPs relate to specific physical sensory stimulation without behavioral involvement, whereas cognitive EPs refer to recordings where the subject has some type of processing task to perform in relation to the sensory input. These potentials are referred to as event-related potentials (ERPs), since they are time-locked to events/stimulation. In clinical neurophysiology, EPs are utilized mainly as a method to assess the functional integrity of well-defined sensory pathways in the primary sensory projection areas of the cortex. Conceptually, ERPs are often regarded as manifestations of specific psychological processes. ERPs can also be evaluated along an exogenous – endogenous axis, but most components seem to be "mesogenous" *i.e.* sensitive to both the physical properties of the stimuli and the nature of the interaction between the subject and the event (Fabiani et al. 2000).

EPs are quantified in terms of the measurement of specific peaks, or positive or negative deflections, thought to represent the main components of the response. These peaks are labelled by their polarity and the nominal latency or poststimulus ordinal latency of the component. Thus, the negative peak at about 100 ms poststimulus is referred to as N100 or N1 (see Figure 1). The earliest of auditory EPs are the otoacoustic emissions which occur within first 10 ms latency and reflect the auditory nerve activity. Cochlear and brain stem potentials can be registered within the first 1–6–8 ms, and they indicate the arrival of sensory input in the cochlea and various auditory nuclei in brainstem. They are followed by the middle-latency auditory components (MAEPs, at latency 8-70 ms), mostly sensory components within the first 100 ms, and the late and mostly cognitive ERPs.

The psychological correlates revealed by a particular ERP study depend on the recording paradigm used: the oddball paradigm, a selective attention task, a memory task or language task, and so on. Technical considerations include procedures to improve the signal-to-noise ratio, removing eye-movement artifacts and other measures

of analysis (the use of difference waveforms, selective averaging, single trial estimates, *etc.*). Hardware requirements should be taken into account as well as compliance issues, which become especially important when clinical patient recordings are planned (Barrett 1992).

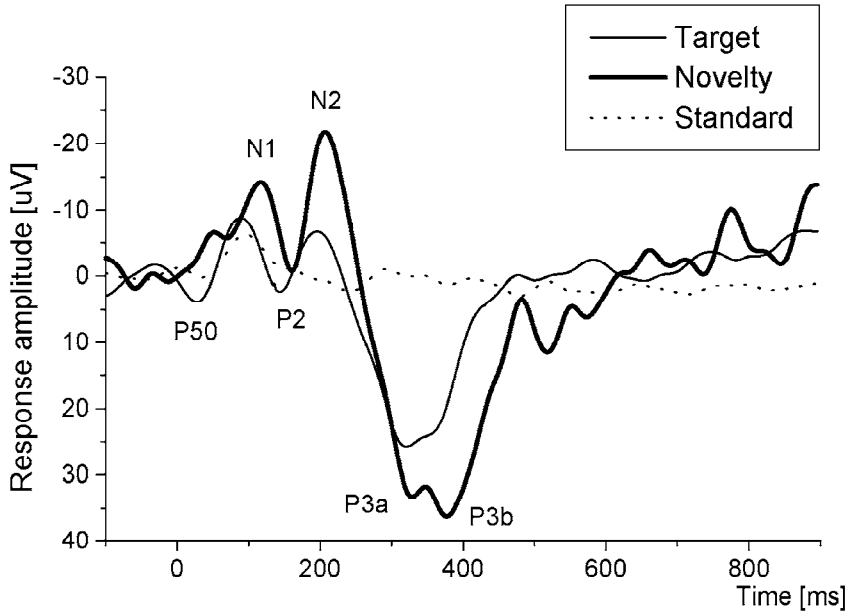


Figure 1. The responses of one healthy control in the Cz channel (central) from an active auditory oddball paradigm. In the figure the P50 component is clearest in the response to a target tone (requiring a button press); the remaining components are clearest in the novelty response (to rare surprising stimuli). The response to frequent standard tones has the lowest amplitude.

A peak in the ERP waveform may represent the summation of several functionally and structurally distinct but overlapping components (Näätänen & Picton 1987). Intervening effects such as the so-called repetition effect and attention effect also have an impact on the component structure, and in the analysis phase different procedures have been developed to overcome these interferences. However, the issues of artifacts, the signal-to-noise-ratio, and other problems of component quantification still need to be considered when making interpretations.

Inferring electrical brain sources of ERPs involve largely similar procedures and problems as referred to in the chapter on the EEG. Mathematical solutions, a combination of other imaging data, invasive methods (single cell recordings and other animal models or intraoperative recordings in humans), and the information gathered from brain lesioned patients are keys to resolving the problems. Current source density maps (also called surface Laplacian or radial current estimate maps) act as spatial filters emphasizing more localized components of sensory ERPs than simple voltage distributions. They can be formed from unaveraged data (epileptic spike) or signal averages. Current source density maps can be interpreted as describing local radial current flow, but they are not as accurate as dipole modeling.

2.4.1. P50 and gating

One of the early components of the cortical response to auditory stimuli, such as clicks, is the P50. When stimuli are presented in a conditioned pair, the P50 component to the second click of the pair is substantially reduced in healthy subjects (the P50 auditory evoked potential conditioning testing). Several investigators have found that in schizophrenia this reduction is deficient, which is interpreted as a dysfunction of normal primary sensory gating (the modulation of incoming signals). On the other hand, there is evidence of intact sensorymotor gating (task-related, requiring a motor response) in schizophrenia at the beginning of the task and deterioration by repetition of the task, further normalized after a brief period of sleep (Griffith et al. 1993). These two forms of gating are, however, separate processes even if they share some properties and findings.

Knight et al. (1989a) have suggested that auditory selection may start at 20-50 ms poststimulus, and that this capacity is controlled by the prefrontal cortex (Chao & Knight 1995), and it has also been shown that P50 suppression is sensitive to acute psychological stressor manipulations (White & Yee 1997). Forebrain activation is particularly related to habituation phenomena and fear potentiation, which are considered forms of behavioral plasticity (Davis 1984, Swerdlow & Geyer 1998).

The startle reflex (*e.g.* the eye blink component in humans) and prepulse inhibition (PPI; the reduction in startle produced by a prepulse stimulus) are also well-known markers of sensory gating. The startle reflex is a constellation of responses to sudden, relatively intense stimuli and is usually classified as a defensive response (Swerdlow & Geyer 1998). Schizophrenic patients have extensive deficits in both startle-related intramodal and crossmodal sensorimotor gating and impairment in PPI as well as habituation of the startle (Geyer et al. 1990, Braff et al. 1992, Gaebel & Wolwer 1992). These markers have been used to create animal models in an effort to develop new medications for psychotic illnesses, since the reflex exists across species (Swerdlow & Geyer 1998).

2.4.2. The orienting reflex

Novel stimuli typically elicit the orienting reflex. The "What is it?" reflex was first discovered by Pavlov in 1927, and the concept was further developed by another Russian scientist, Sokolov, who interpreted the OR within a cognitive context as a central comparison device in the brain that compares input with stored representations. Sokolov also distinguished the OR from other related types of reflexes such as the defense reflex (DR) and specific adaptive reflexes. He considered the OR's functional significance to be the tuning of neural systems for sensory analysis "to ensure optimal perception of the stimulus". The OR comprises motor components (arrest of ongoing behaviour, directing receptors towards the stimulus), autonomic responses (cardiovascular, electrodermal, pupil diameter), electrocortical (EEG alpha blocking), and respiratory changes. In the case of stimulus repetition the stimulus becomes

familiar, and there is no need to allocate attentional resources to it, so each component and variable habituates (diminishes and disappears) at its own habituation rate. Generally, the course of habituation of the OR can be described as an exponential decrease over trials, and there are several methodological possibilities to describe and quantify its degree. In contrast, the DR may even increase following repeated stimulus presentation, and OR, too, can sometimes exhibit dishabituation (Sokolov 1975, Sabalesky et al. 1990, Sokolov 1990, Öhman et al. 2000).

2.4.3. N1 wave of the human auditory evoked potential

The N1 is the most prominent auditory event-related response. It indexes the detection of sound, but also overlaps with non-specific arousal activity (Näätänen & Picton 1987). It is elicited by any change in the acoustic environment, and it is largest in response to the first stimulus after a period of silence. The orienting-reflecting non-specific component lies in the vertex, but the N1 reaches its amplitude maximum in the primary auditory cortex.

The scalp-recorded auditory elicited complex around 50-150 ms potentially reflects the activity of at least six different generators: a component generated in the auditory cortex on the supratemporal plane, a component generated temporoparietally in the association cortex, components from motor and premotor cortices, the mismatch negativity, a temporal component of the processing negativity, and a frontal component of the processing negativity (Näätänen & Picton 1987). Mismatch negativity and processing negativity are not parts of the N1 in essence; instead they depend more on the conditions under which the stimulus occurs and they have a considerably longer phasic duration than the N1 (Näätänen & Picton 1987). Thus, the N1 consists of three components, which are mainly controlled by the physical and temporal features of the stimulus, and by the general state of the subject. These components have different sensitivities to stimulus features and state factors and different source locations. According to McCallum and Curry (1980), the N1a wave reaches its maximum at about 75 ms at temporal and frontal-pole electrodes, N1b has a mean peak latency of 106 ms

and an amplitude maximum at central electrodes corresponding to the vertex response, and N1c from temporal electrodes at a peak latency of 129 ms (Näätänen & Picton 1987). The N1 appears to contain both stimulus-specific and stimulus-nonspecific components and its amplitude decreases but latency increases at lower stimulus intensities.

The N1 component has been reported to be depressed in several schizophrenia studies. In some studies the N1 has been measured as N1-P2 amplitude, while others have shown attenuation of the P2 component amplitude. The N1 amplitude decrement in medicated schizophrenia patients did not reveal any changes according to stimulus probability, task-demands or oddball targets, whereas the task-related P2 latency increase was greater in healthy controls (O'Donnell et al. 1994). In another report the N1 amplitude decrement in schizophrenia was reported to be associated with several interstimulus intervals (ISIs), but the degree of deficit increased with increasing ISI (Shelley et al. 1999). When schizophrenic patients were compared with healthy controls and patients with schizotypal personality disorder, there was an amplitude attenuation in N1 in schizophrenic, but not in schizotypal patients (Trestman et al. 1996). The disorganised/undifferentiated subgroup of schizophrenia appeared to be less sensitive to the N1 decrement (Boutros et al. 1997).

2.4.4. Mismatch negativity and N2b

The N1/P2 component is followed by another negative component termed N2. This can be further divided into N2a, or mismatch negativity (MMN; (Näätänen 1982)), which is a significant part of automatic processing, and N2b, which has a role in the controlled auditory discrimination process ("noticing the sound") (Picton 1995). The MMN waveform is generated by a mismatch between a deviant sensory input and a sensory memory-trace representing the standard stimuli (Alho 1995, Näätänen 1995, Näätänen & Alho 1995a, Näätänen & Alho 1995b, Näätänen & Alho 1995c, Lang et al. 1995). It reflects automatic, preattentive auditory discrimination and has an important role in the involuntary switching of attention to a large or salient stimulus

change outside the focus of attention (Alho 1995). MMN can be elicited by the frequency, intensity, complexity, and duration deviant stimuli (Alho 1995). Three variables are important when determining whether patients exhibit a reduced MMN to frequency deviants: the deviant probability, the degree of deviance and the interstimulus interval (Michie et al. 2000). During the last few years MMN has been the most studied ERP component in schizophrenia research.

The major neuronal generator of mismatch negativity is in the supratemporal auditory cortex bilaterally (Alho 1995), but other parts of the brain also contribute to the scalp-recorded MMN. The activity in the frontal lobes reflects a call to switch attention and activates further processing of the previously unattended stimulus (Näätänen 1995). The exact cerebral location of the dominant neuronal source of MMN depends on the stimulus feature (Giard et al. 1990, Paavilainen et al. 1991, Alho 1995, Csepe 1995). Scalp distribution, MEG data, intracranial recordings and brain-lesion data suggest that, in addition to temporal generators, frontal and deep (thalamic, hippocampal) MMN sources also exist (Alho 1995), and there appears to be a right hemisphere dominance (Paavilainen et al. 1991). Evidence for an additional right inferior temporal generator further supports the hypothesis of right hemispheric dominance in early sound discrimination (Waberski et al. 2001). More recently, two sources were found in the frontal lobe (left cingulate and right inferior frontal cortex) similarly placed for duration and pitch deviancy MMN, and were well replicated on retest (Jemel et al. 2002). The cingulate generator is activated later than the temporal ones, which supports the hypothesis of a frontally located mechanism of involuntary switching of attention triggered by the temporal change detection system (Waberski et al. 2001, Jemel et al. 2002).

The N2b differs from MMN in that it is attention-dependent and the template for the comparison process may be actively generated by the subject, reflecting "noticing the sound" (Fabiani et al. 2000). The N2b has been reported to be largest for rare stimuli and several types of N2s can be described even within the same modality (Fabiani et al. 2000). Since the N2 component also covaries with reaction time, it has been used in mental chronometry studies (See chapter on P3) (Fabiani et al. 2000).

The attenuation of MMN has been observed in several studies in the previously medicated and/or chronic phase of schizophrenia (Shelley et al 1991, Javitt et al 1993, Catts et al. 1995, Javitt et al. 1995, Matsuoka et al. 1996, Oades et al. 1997, Alain et al. 1998, Umbricht et al. 1998, Kasai et al. 1999, Kreitschmann-Andermahr et al. 1999). Kathmann et al. (1995b) and O'Donnell et al. (1994) found no difference in the amplitudes of MMN and Hirayasu et al. (1998) only a laterality change more evident in the left hemisphere in the early phase of illness. Michie et al. (2000) demonstrated attenuation in duration-MMN deviants and more recently Kasai et al. (2002a) showed impairment in frontotemporal attenuation of the MMN process in relation to speech sounds. These findings were supported by British investigators, who found an impairment in frontal but not temporal components of MMN in schizophrenia (Baldeweg et al. 2002). Attenuation of the N2b is a less frequently discussed extra finding in MMN reports on psychotic illnesses (Kasai et al. 1999).

Concerning specificity, the deficit has been demonstrated to reach a maximum under conditions where MMN is normally greatest (Javitt et al. 1998) and the pattern of MMN differs from that observed in Alzheimer's disease, stroke, alcohol intoxication (Javitt et al. 1998) or obsessive compulsive disorder (Oades et al. 1997). Furthermore, the first-degree relatives of schizophrenic patients have exhibited MMN amplitude reduction (Jessen et al. 2001).

Javitt et al. (1995) found no significant difference between medicated and drug-withdrawn subjects and no correlation between the prior neuroleptic dosage or length of the drug-free period and the MMN amplitude. The processing negativity was also identical in medicated and drug-withdrawn subjects (Javitt et al. 1995). Using an animal model of MMN (monkeys exhibit a similar response), and based on NMDA antagonist induced attenuation in MMN, Javitt et al. (1996) suggested that a widespread cortical deficit in NMDA (N-methyl-D-aspartate) receptor-mediated neurotransmission might account for some memory impairment in schizophrenia. It has also been reported that ketamine induces impairments in MMN amplitude and CPT performance in healthy volunteers (Umbricht et al. 2000). A recent report suggested that chronic administration of anxiolytics and hypnotics has no effect on

MMN amplitude, topography or latency (Kasai et al. 2002b), and earlier it was shown that clozapine has no effect on MMN or the N2 (Umbricht et al. 1998).

2.4.5. P3a – novelty processing

The positive ERP component elicited by a surprising or unexpected stimulus with a scalp-recorded maximum at fronto-central electrodes is called the P3a, a subtype of the P3. It has a 60-80 ms earlier peak latency than the P3b component and undergoes rapid habituation following 5-10 stimulus repetitions (Knight & Nakada 1998). Interestingly, this habituation phenomenon seems to decrease with ageing, and older subjects or subjects with frontal lobe damage may therefore have problems in forming or maintaining a stimulus template (Fabiani et al. 2000). The P3a is often accompanied by a sympathetic skin reaction, and the simultaneous P3a amplitude is larger than that without SSR orienting (Friedman et al. 2001). It has been suggested that MMN might serve as a call for an attention switch and is followed by a P3a component (representing the attention switch) in case a potentially significant background event turns out to be sufficiently deviant (Friedman et al. 2001).

A classical oddball paradigm can be used to elicit the P3a (either the passive type, where the attention of the subject is directed away from stimuli, or the active type, where the subject must pay attention to target stimuli). Another means of eliciting the P3a is the so-called novelty oddball, where three classes of stimuli are used: high probability standards, low-probability targets/deviants and randomly presented stimuli that are unique, surprising and novel. It has been suggested that the stimulus context determines the P3a and P3b in a three-stimulus paradigm (Katayama & Polich 1998).

Previous reports on the P3a and psychotic illnesses share the same findings as those concerning the P3b, partly since the majority of articles have only determined one P3 component and/or the results of both components have been reported in an integrated manner. Thus findings concerning novelty processing and the P3a remain unclear. Schizophrenic patients have reduced frontal and parietal P3 amplitudes and their healthy siblings show a reduction only in the frontal P3 compared to healthy control

subjects (Turetsky et al. 2000).

2.4.6. P3b – target relevance

The P3 or P300 (referred to in this summary as the P3b to distinguish it from the novelty P3a) is a positive ERP that usually occurs between 300-500 ms poststimulus, reaching its maximum at posterior parietal scalp locations (Fabiani et al. 2000). It is elicited when a stimulus is relevant to a task. The generators of the scalp-recorded P3 remain somewhat controversial, probably because of its long latency and diverse cognitive nature. It has been suggested that the P3 represents the summation of activity from multiple generators located in widespread cortical and possibly subcortical areas (Knight et al. 1989b, Tarkka et al. 1995, Knight & Scabini 1998). Bilateral sources appear to be in the medial-temporal lobes, and there is evidence from lesion-data that the temporo-parietal junction has a role in P3 generation (Knight et al. 1989b, Tarkka et al. 1995). Interestingly, the scalp topographies of the P3 are somewhat distinguishable between different cognitive processes (*e.g.* button press *vs.* withholding the response) (Pfefferbaum et al. 1989).

The P3 can be elicited in any modality and with diverse stimuli. Indeed, it has been related to processing resources demanded by the task. Similarly, the P3 latency may reflect the stimulus evaluation/categorization time (Fabiani et al. 2000). Accordingly, the P3 latency has been used to supplement reaction-time measures in so-called mental chronometry studies, where decision-making processes are of interest. Moreover, the subject's future strategy as revealed by overt behavior can be predicted from the P3 response (Fabiani et al. 2000).

The P3 component of ERPs has been reported to be attenuated in schizophrenia (Kidogami et al. 1991, McConaghy et al. 1993, Shelley et al. 1996, O'Donnell et al. 1999, Kimble et al. 2000, Mathalon et al. 2000a). P3 amplitude deficits have been reported in relatives of schizophrenic patients and in schizotypal subjects as well as in different stages of medication and the disease process, and concerning different sensory

modalities, psychometrics and semantic processing (Kidogami et al. 1991, Adams et al. 1993, Kochi et al. 1996, Frangou et al. 1997, Klein et al. 1999, Kimble et al. 2000, Mathalon et al. 2000a, Mathalon et al. 2000b). It has been suggested that patients with more negative symptoms of schizophrenia might have the greatest decreases in P3 amplitude (McConaghy et al. 1993, Williams et al. 2000). Recent findings suggest that clozapine improves attention-dependent information processing observed in P3, but does not ameliorate preattentive deficits (Umbricht et al. 1998). P300 deficits and failures of selective attention have been unequivocally confirmed as signs of schizophrenia in dozens of previous works (O'Donnell et al. 1999). It is regarded as a potential vulnerability marker for schizophrenia when used in conjunction with other neuroimaging and neuropsychological testing methods (Andreasen 1999, Bharath et al. 2000). However, changes in P300 occur in several (neuro)psychiatric conditions (Sandman et al. 1987, Himani et al. 1999, Chen et al. 2001, Mochizuki et al. 2001, Anderer et al. 2003, Katada et al. 2003, Pokryszko-Dragan et al. 2003), suggesting that the role of P300 alterations is rather a non-specific indicator of an illness involving selective attention problems.

2.4.7. Different forms of attention

One of the main functions of attention is to filter out unnecessary information and sharpen our perception of the things we are attending to (Barinaga 1997). It provides a compact representation of currently important external information and makes it accessible to planning (Barinaga 1997) and other higher cortical functions. Thus, it can be conceptualized as a selective mechanism for gating sensory information and/or a mechanism for the appropriate allocation of processing resources to relevant stimuli (Banich 1998, Coull 1998).

One can attend to objects, locations, or movements in time and in several different ways. Attention comprises several sub-processes (see Coull, 1998): 1) attentional orientation, *i.e.* the simple direction of attention to a particular stimulus, 2) selective or focused attention, *i.e.* giving attentional priority to one stimulus in favour of another, 3)

divided attention, *i.e.* dividing attention between two or more different stimuli, and 4) sustained attention or vigilance, *i.e.* attending to one stimulus over an increasing period of time. Attention is a multidimensional psychological process and it interacts closely with other processes, *e.g.* arousal (Coull 1998). It does not generate any unique potentials of its own, but acts to modulate stimulus-induced ERPs (N1, P3 *etc.*), usually by enhancing the amplitudes (Coull 1998). It is distributed across both space and time. The essential meaning of arousal (both low level physiological and high-level cognitive) is that it determines the attentional capacity and, together with the required effort for processing the stimulus, sets the extent to which a stimulus is processed (Coull 1998).

Being a diverse phenomenon, the cerebral sources of attention control are not fully known. The anterior cinglum and thalamus play an important mediating role (Portas et al. 1998). Fronto-temporal circuits and centroparietal activations have been suggested as well as the hippocampus and corpus callosum, which emphasizes the importance of interhemispheric connections and the division of labor for parallel processing (Banich 1998).

Knight summarizes (1984) the importance of proper prefrontal control mechanisms of attention by describing a person with an affected prefrontal lobe: "The inability to gate irrelevant inputs coupled with deficits in novelty detection impairs the coding of the beginning and end of discrete events. Information is stored and retrieved with incorrect spatiotemporal tags. This results in a person who lacks a coherent past or future and is locked into an uncertain present."

2.4.8. Visual evoked potentials

The visual system can be studied by observing many different phenomena. Oculomotor functions can be assessed using the amount/amplitude characteristics and initiation of smooth pursuit eye movements, predictive pursuit (visual target disappears randomly), eye fixation parameters, visually guided saccades, remembered saccades, and antisaccades (Radant et al. 1997). There are deficits in these measures in schizophrenia,

which have been associated with neuropsychological performance problems (Radant et al. 1997). The typically increased blink rate in schizophrenia has been demonstrated to be normalized following drug treatment (Mackert et al. 1990, Mackert et al. 1991). Eye tracking and smooth pursuit eye movement impairments are one of the most robust findings of biological correlates for schizophrenia, and they are related not only to attention and information processing deficits in the frontal lobe connections, but also subcortical contributors and cerebellar influences (Pivik et al. 1988, Pivik 1991).

Visual event-related potentials can be elicited by simple visual stimuli (light flashes) or by complex objects (*e.g.* geometrical objects). A widely used paradigm to study the sensory visual ERPs is the reducing-augmenting procedure (Bucshbaum 1968), although it has also been critisized for its methodological limits (Katsanis et al. 1996). Subjects are exposed to light flashes of four different intensities while their vertex ERP is recorded. Irrespective of the method used to elicit visual ERPs, the components that occur between approximately 50 and 260 ms following stimuli at central scalp locations are influenced by both physical properties of the stimuli and the amount of selective attention allocation (Straube & Oades 1992). A negative peak at the latency of 100-140 ms poststimulus is called the N1, a positive peak at about 100 ms the P1 and another at 200 ms the P2. The P3 and MMN components are also often reported, corresponding to those described in relation to auditory modality. These components show considerable variation across subjects, but are usually identifiable.

Various controversial alterations of latency, component configuration, and laterality have been reported in visual event-related potentials (ERPs) elicited by simple visual stimuli in psychotic illnesses (Gruzelier et al. 1993, Matsuoka et al. 1996, Jin et al. 1998, Van Sweden et al. 1998). However, in first-episode patients and their relatives, no significant alterations have been observed during early visual processing (Katsanis et al. 1996). Moreover, the late positive component of the visual ERP has been reported to be sensitive to medication (Mintz et al. 1982, Mintz et al. 1995). On the other hand, the negative component differences were more prominent in medicated schizophrenic patients during remission (Matsuoka et al. 1996). Findings concerning the P3 were summarized in the previous three chapters of this summary.

2.4.9. Face-recognition and ERPs evoked by faces

Face recognition is crucial for ethological survival, while a proper response to facial expressions plays an important role in social competence. In psychosis, misinterpretations of social interactions are common and often related to delusional misidentifications or aberrations of perception. Although it is known that the processing of simple visual stimuli seems to be intact in early psychosis (Katsanis et al. 1996), so far no reports have been published concerning the processing of face stimuli or complex visual stimuli in acute psychosis.

Face-specific electrophysiological brain responses were first identified in single-unit studies in monkeys (Perret et al. 1982, Baylis et al. 1985), and later in ERP studies of human subjects (Bötzel & Grusser 1989, Jeffreys et al. 1992, Seeck & Grusser 1992). More recently, two sources of face-specific processing have been suggested by non-invasive MEG data from normal human subjects (Halgren et al. 2000). The fusiform gyrus selectively encoded faces at 165 ms, and a midline occipital source distinguished happy and sad faces (Halgren et al. 2000). While many complex visual objects can activate the fusiform gyrus, the temporo-spatial distribution of the activity during facial emotion recognition is particularly distinguishable (de Gelder et al. 1999, Morris et al. 1999) for both simple face recognition (Sams et al. 1997) and for the processing of abstract visual stimuli (Scalaidhe et al. 1999).

Bentin et al. (1996) identified an early face-specific negative ERP (N170) with noninvasive scalp-recordings, with the largest ERP being observed at posterior temporal leads, T5 and T6, over the right hemisphere. The N170 has been linked to late stages of structural encoding or face configuration analysis for further recognition processes (Eimer 2000b) rather than reflecting the activity of the "eye processor", though it can be elicited by heads or single facial features as well (Eimer 1998). The N170 seems to mature gradually and quantitatively throughout childhood between the ages of 4-14 years (Taylor et al. 1999), and eye processing may develop before face processing (Taylor et al. 2001). In developmental prosopagnosia, the N170 component showed no specificity to faces (Bentin et al. 1999a, Eimer 2000a). Although gender processing has

no effect on the N170 (Mouchetant-Rostaing et al. 2000b), other ERP components have been used in an effort to distinguish the processing stages involved in face perception and recognition. The N400 and P600 components are related to face recognition, which may even be disrupted by impaired encoding (Eimer 2000a). Before the N170, the vertex-positive scalp potential (VPP) was found to be evoked by faces and other objects (Jeffreys & Tukmachi 1992). The VPP appears to be optimized to single fixated faces (Jeffreys et al. 1992) and influenced by stimulus orientation (Jeffreys 1993).

The cerebral spatial organization of recognizing faces and emotional facial expressions in faces has been elucidated by several recent intracranial ERP (event related potential) studies (Allison et al. 1999, McCarthy et al. 1999, Puce et al. 1999). In fMRI and PET/SPECT studies, face recognition, expression and color have been reported to activate distinct parts of the fusiform gyri (Allison et al. 1994a, Allison et al. 1994b, Kapur et al. 1995, Puce et al. 1995). In addition to fusiform and parahippocampal areas, the prefrontal cortex contains face-specific neurons. Besides the well-characterized anatomical and functional asymmetries of the frontotemporal areas in schizophrenia (Goldman-Rakic 1999, Goldman-Rakic et al. 2000), anomalous asymmetry of the fusiform and parahippocampal gyri gray matter has also been recently found in a postmortem study of patients with schizophrenia (McDonald et al. 2000).

Numerous reports indicate that schizophrenia impairs both face and facial expression recognition at the behavioral level (Gaebel & Wolwer 1992, Mueser et al. 1997, Shaw et al. 1999). The chronicity of the illness, but not the medication status, is related to poor performance in affect recognition tests (Mueser et al. 1997) in both acutely ill and partly remitted schizophrenia patients (Streit et al. 1997). Chronic patients tend to perform poorly in both the Test of Facial Recognition (Ryan et al. 1988) and affect perception tasks (Kerr & Neale 1993), suggesting a generalized impairment in facial perception. These neurocognitive deficits show trait-like characteristics which remain stable over time and are not related to psychopathology or medication (Gaebel & Wolwer 1992, Lewis & Garver 1995, Wolwer et al. 1996). In psychotic illness, strong associations have also been reported between performance failures in face recognition and attention tasks (Addington & Addington 1998).

However, intact facial affect recognition has also been reported in schizophrenia outpatients (Leentjens et al. 1998) and schizotypal subjects (Toomey & Schuldberg 1995). Moreover, the psychotic symptoms of inappropriate affect (Shaw et al. 1999), bizarre behavior and negative symptoms were connected with facial affect recognition and overall neuropsychological functioning (Schneider et al. 1995). However, other studies have reported that neither affect expression nor symptoms of affect pathology, like blunted affect or mood swings, are related to face recognition performance (Sweet et al. 1998, Shaw et al. 1999).

2.4.10. Summary of previous ERP findings in psychotic illnesses

The most consistent abnormality is a reduction in the P3 amplitude in psychotic illnesses. The amplitude maximum of the P3 component may also occur more anteriorly and displaced to the right in patients when compared with that of healthy controls, and it seems to be independent of potential reaction time deficits (Barrett 1992). The P3 findings and asymmetries have been related to overall pathology of the left temporal lobe in schizophrenia and misconnections in cortico-cerebello-thalamo-cortical circuitry (CCTCC).

The reduction in amplitude of several ERPs (N1, MMN, N2) before the P3 shows that cognitive deficit associated with schizophrenia is present early in the chain of cognitive events, not just in the P3 (Pfefferbaum et al. 1989), and it is widely spread extending to complex neural networks. Moreover, localization studies have demonstrated that the N1, MMN and P3 have separate electrical sources in the brain. Thus the impairment also affects the sensory cortex, and it appears that brain dysmorphology in psychotic illnesses is both diffuse and expansive (Javitt et al. 1995).

2.4.11. Other ERP components

Several ERP components are not dealt within this summary, although they probably also have important implications in the study of psychotic illnesses. Contingent negative

variation (CNV) is one example of ERPs associated with preparatory and movement related processes and anticipation, which have been demonstrated to be abnormal or distracted in schizophrenia (Rohrbaugh et al. 1986, Wagner et al. 1996). The possible alterations in auditory middle latency ERPs and other early components may turn out to be important as well. Furthermore, later components such as language-related components, the most common of which is the N400, elicited with word congruency/incongruency tasks, has repeatedly been demonstrated to be attenuated in schizophrenia (McCarley et al. 1991, Adams et al. 1993, Andrews et al. 1993, Niznikiewicz et al. 1997, Matsuoka et al. 1999, Kimble et al. 2000). The so-called slow waves (exceeding 400-500 ms) will be of at least theoretical interest in the future, since their properties, generators and psychological or behavioral content remain largely unknown, except perhaps processing negativity (Näätänen 1982).

2.5. Neuropsychology – memory, language and learning in psychosis

Traditional psychological testing of the projective type (*e.g.* Rorschach) is not often informative in evaluating the functional level and diagnostics of a schizophrenia patient, but it sometimes remains useful in an effort to find out the implications of impaired reality-testing. Neuropsychological testing may instead become a standardized element in the clinical diagnosis of psychotic illnesses, useful for subtyping and investigational correlations (Lipton & Cancro 1995). It is typically useful in identifying pathological processes involving attention, memory, executive functions, language and motor functions. In chronic schizophrenia, the neuropsychological profile often resembles that of brain-damaged patients (Lipton & Cancro 1995), probably partly associated with medication or drug-effects. Indeed, patients with schizophrenia-like psychoses of epilepsy and schizophrenia had almost identical neuropsychological performance profile (Mellers et al. 2000).

Attentional deficits, especially those of selective attention, have been found in particular in non-paranoid schizophrenia. These deficits are not related to the chronicity of illness, but are related to prefrontal functions. Impairment of the working memory has been reported in schizophrenia (Strandburg et al. 1990, Carter et al. 1998) at least partly independent of deficits in attention, motivation, or cooperativeness. These impairments affect both chronic and first-episode patients and the relatives of schizophrenia patients, and they have been related to prefrontal cortex dysfunction in fMRI (Park & Holzman 1992, Park & Holzman 1993, Goldman-Rakic 1994, Park et al. 1995, Perlstein et al. 2001). The planning, sequencing, concept formation, cognitive set-shifting, and maintenance of responses to environmental cues have been reported to be disturbed in schizophrenia (Lipton & Cancro 1995), all of which are suggestive of abnormal prefrontal cortical function domains (working memory, executive functions and inhibitory control) (Fuster 1997). Thought process disturbances are regarded as secondary symptoms of schizophrenia. Slowing of the reaction time and pathology in eye tracking and saccades are frequently even clinically observed findings related to schizophrenia. Women with schizophrenia seem to perform significantly worse in verbal memory, spatial memory and visual processing than men and have significantly poorer right than left hemisphere performance (Lewine 1996).

One of the most frequently used tests to reveal prefrontal functions, attentional deficits and working memory capacity is the Wisconsin Card Sorting Test (WCST), and since two versions of the test were used in the current project, it is the one explained here in favour of others. The classical WCST requires participants to sort a series of cards into one of four key cards that vary in shape, color, and number. Participants use feedback (correct or incorrect) to ascertain the correct matching rule, which shifts after 10 consecutive correct responses. Patients with schizophrenia achieve fewer categories and make more perseverative errors than healthy volunteers (Williamson et al. 1989, Mattes et al. 1991, Sullivan et al. 1993, Glahn et al. 1999), and the nonparanoid subgroup seems to perform worse than the paranoid patients (Rosse et al. 1991).

The Stroop test is also frequently used to measure frontal lobe functions and attentional processes demonstrating performance deficits in schizophrenia. Analysis

methods and conclusions based on the Stroop test have raised questions (Schooler et al. 1997a, Schooler et al. 1997b, Elvevåg et al. 2000). When deficit *vs.* nondeficit forms of schizophrenia were compared in frontal lobe tasks, the former performed worse, but in temporal lobe tasks there were no differences (Buchanan et al. 1994). Frontal, thalamic and cerebellar regions may constitute a circuit that is important in the performance of a variety of memory tasks.

General intellectual impairment seems to be an important determinant of poor language test performance in schizophrenia, but the presence of a formal thought disorder may also contribute. Both linguistic impairment and formal thought disorder were related to a high-order semantic deficit (Moritz et al. 2001, Rodriguez-Ferrera et al. 2001), and the deficit was reported to be independent of medication effects with no association in positive psychosis symptoms (Condray et al. 1995). Semantic processing related to ERP abnormalities (N400) has confirmed the attention deficit disturbances in chronic schizophrenia (Adams et al. 1993). In the classification learning test, schizophrenic patients improved their categorization performance to a similar extent as the controls, but they failed to recognize the category cues; they were able to establish the categories, but the result remained unconscious (Keri et al. 2000).

Some cognitive tasks have been identified as trait-linked markers of schizophrenic disorder: reaction time crossover, backward masking, dichotic listening, serial recall tasks, vigilance tasks requiring high processing loads, and span-of-apprehension tests with large visual arrays. Deficits in these areas have been explored in a large number of cognitive studies examining various aspects of processing (Siegel 1995). Ilonen et al. (1999) have studied neuropsychological functioning in Finnish first-episode and prodromal sign patients with schizophrenia, bipolar disorder, psychotic depression and severe non-psychotic depression using a comprehensive neuropsychological test battery. Her results showed similar cognitive impairments (*e.g.* lower full-scale IQ) in schizophrenia and in psychotic depression, whereas patients with bipolar disorder only had difficulties in complex attention, psychomotor speed and executive functions. All patients had mild to severe difficulties in these tasks when compared to healthy controls. (Ilonen 1999)

2.6. Brain imaging studies – anatomy, functional imaging, neurotransmitters

The following cursory overview of imaging data concerning psychotic illnesses is included in the current thesis as a reminder of the complexity and multi-level nature of the mental phenomena and of the diversity of methodologies used to address the same problem from several different, yet overlapping, point of views. The aforementioned problem of heterogeneity in patient samples is confirmed by all imaging methods. Interestingly, the same brain areas that are known to be important in information gating, orienting (posterior parietal cortex, striatum, superior colliculus, thalamic pulvinar, reticular system) and attentional (anterior cingulate, dorsolateral prefrontal cortex, thalamus and fronto-parietal areas) modulation seem to be involved in most imaging studies of psychotic illnesses (Coull 1998).

2.6.1. Anatomy

As early as 1915, Southard showed that most prominent anatomical abnormalities in schizophrenic brains were situated in left association cortices (Harris & Hoehn-Saric 1995). This eventually led to theories of cell migration defects during development. Another classical finding of the anatomy of schizophrenia is the enlargement of cerebral ventricles, which has also been related to cortical atrophy and developmental theories. Later came findings of alterations in heteromodal association cortices, in particular in three major association areas (dorsolateral prefrontal cortex, superior temporal gyrus, and inferior parietal lobe). These regions have rich reciprocal connections and they participate in higher coordination and modulation of sensory, motor and behavioral functions, all of which are obviously disturbed in psychosis. These regions undergo the final pruning and myelination during adolescence at the time when the incidence of psychotic illnesses is high. The cortical anomalies have been verified using neuropathological methods, by CT (computerized tomography) and more recently by MRI (volumetric studies of different structures and grey matter/white matter ratios,

gyrography technique *etc.*) (Zipursky et al. 1998). Morphometric studies have suggested neuronal atrophy as the anatomic substrate of schizophrenia based on the finding of an abnormally high neuronal density in the cortex of the schizophrenic brain (Selemon et al. 1995).

In addition to cortical deficits, alterations in basal ganglia, limbic structures, the anterior cingulum, thalamus and cerebellum have been related to psychotic illnesses. Important findings have also been the absence of regional hemispheric volume asymmetries in first-episode schizophrenia (Bilder et al. 1994), the inversion of the hemispheric laterality of the anterior cingular gyrus in a neuropathological sample of schizophrenia (Albanese et al. 1995), and the reversal of asymmetry of the planum temporale (Petty et al. 1995). In their recent report, Collinson et al. (2003) showed that the total brain volume was significantly smaller in the group with early-onset disease, especially for the left hemisphere in males. The female patients had significantly reduced rightward asymmetry, whereas the male patients tended to have reduced leftward asymmetry (Collinson et al. 2003). Furthermore, the decreased left hemisphere volume in males and decreased rightward hemispheric asymmetry in females correlated with reduced IQ (Collinson et al. 2003).

2.6.2. Functional imaging - PET, SPECT, MEG and fMRI studies

Functional imaging has been used to study cerebral blood flow and metabolism both at baseline, or in resting conditions, and during different motor, sensory or cognitive activations and, for example, during active hallucinations in psychotic illnesses (Silbersweig & Stern 1996).

Abnormal functioning of the frontal lobes has been reported in several studies using different techniques (WCST, Stroop). Patients seem to lack the increasing activity-induced increase in cerebral blood flow and metabolism in the dorsolateral prefrontal cortex during a frontal task. Moreover, functioning of the frontal lobe correlated positively with the task performance and the abnormality was not affected by

antipsychotic medication. Similar alterations were additionally detected in relatives of schizophrenia patients. There are also implications of a correlation between hypofrontality and negative symptoms. (Weinberger et al. 1986, Rubin et al. 1991, Buchsbaum et al. 1992, Weinberger et al. 1994, Harris & Hoehn-Saric 1995) Many of these findings are interpreted as supporting the so-called hypofrontality theory of schizophrenia and are also in line with the recent findings of abnormal development of dopamine innervation in the prefrontal cortex (Finlay 2001). However, several studies performed at rest have reported normal frontal lobe functioning in schizophrenia (Weinberger et al. 1994). Moreover, never-medicated patients with an illness duration of less than 2 years exhibited increased frontal lobe glucose metabolism compared with controls (Harris & Hoehn-Saric 1995).

Other cortical structures (temporal and parietal lobe association cortices and mesial temporal limbic structures) have also been functionally impaired in imaging studies of schizophrenia, as noted earlier concerning anatomical studies. Alterations in functional laterality have been found in schizophrenia with indications of the reversal of normal asymmetries in the primary auditory cortex (with MEG) (Reite et al. 1989, Tiihonen et al. 1992, Reite et al. 1997, Tiihonen et al. 1998, Pekkonen et al. 1999), but abnormally lateralized activity has also been observed during other activations (Van Horn et al. 1996, Tzourio et al. 1997). A reduced PET glucose metabolism in the inferior and medial frontal lobe has been reported in never-medicated patients during acute psychotic episodes (Buchsbaum et al. 1992, Clark et al. 2001). In contrast to hypofrontality, the temporal lobe functions seem to be enhanced, including hyperactivity in the area of the auditory association cortex in the superior temporal gyrus, normalized by clinical improvement. Concerning laterality, the left-side dominance in pathological findings seems to be correlated with psychopathology (PET; (DeLisi et al. 1989)). Findings in relation to the hippocampus are controversial, as both hypo and hyperactivity have been related to schizophrenia (Harris & Hoehn-Saric 1995, Yurgelun-Todd & Renshaw 1999).

More recently, a combination of imaging techniques has revealed interesting results. Patients with schizophrenia had limbic-anterior cingulated hypoperfusion during

attentional tasks (Yucel et al. 2002). It has also been suggested that medication (olanzapine) may affect the functional interactions between the neural activity of the cerebellum, thalamus and prefrontal cortex (Stephan et al. 2001).

2.6.3. Neurotransmitters

Considerable attention has focused on the influence of dopamine system imbalance in psychotic illnesses. This began with the findings of psychoses induced by dopaminergic drugs and the fact that antipsychotic drugs are dopamine antagonists. These coincidences do not mean, however, that dopamine necessarily has a key role in the ultimate pathophysiology of psychotic illnesses. Nevertheless, there is evidence of dopamine effects on the signal-to-noise ratio in information processing (Daniel et al. 1991, Mattay et al. 1996). Abnormalities in dopamine D2 receptor density in the striatal area in schizophrenia have been demonstrated in several imaging studies, and the densities have been found to be increased independently of psychotropic medication. Some controversies still exist in relation to these findings (Harris & Hoehn-Saric 1995). More recently, the interest in dopamine metabolism has also focused on extrastriatal brain areas.

Direct evidence of a hyperdopaminergic state in schizophrenia has been difficult to demonstrate, given the difficulty to measure dopamine transmission in the living human brain (Laruelle et al. 1997). Findings of amphetamine-induced dopamine release have demonstrated a dysregulation of dopamine in schizophrenia (Laruelle et al. 1999). In all studies, a large variance was observed within the schizophrenic group, but dysregulation of dopamine is present at never-medicated onset of illness, and in patients with a relapse, but not in patients studied during a remission phase (Laruelle et al. 1999).

Dopaminergic modulation may play a key role in working memory functions and attentional processes that require a high degree of executive control, such as attentional set-shifting (Coull 1998). A reduction in dopamine activity in the dorsolateral prefrontal cortex leads to impaired performance in working memory tasks and an impairment in

attention shifting from one domain to another (Coull 1998).

Concerning attention modulation, animal studies have revealed that noradrenergic activation helps to focus attention on task-relevant behaviors by attenuating the distractibility (Coull 1998), suggesting that noradrenaline is necessary for accurate attentional performance under arousing circumstances. In humans the α2 drugs affect arousal and attention, possibly mediated by the frontal cortex (Coull 1998). It is possible that noradrenergic functions play an important role in different levels of attention control through discrete brain regions (Coull 1998). On the other hand, there is evidence that the effect of clonidine on thalamic activity is dependent on the underlying arousal of the subject (a low state of arousal leads to a strong drug effect). Interestingly, dopamine and noradrenaline seem to have complementary roles in attention modulation, the former being active in the lower arousal mechanism (response likelihood and speed) and the latter in the upper arousal system (response selection) (Coull 1998). There is also evidence that noradrenaline is more related to stress, novelty and sensory alerting processes and dopamine to rewarding stimuli, which are known to increase the arousal level (Coull 1998).

Cholinergic dysfunction is often associated with the impairment of long-term memory functions, but it also increases the speed and accuracy of a sustained attention performance task. It has also been demonstrated that nicotine enhances the attentional function of Alzheimer patients (Coull 1998). It has been suggested that muscarine and nicotine receptor agents have complementary roles in attention control: nicotine is related to visuo-spatial shifts and muscarine to the levels of attention and arousal (Coull 1998). Cholinergic manipulations affect both memory and attention, possibly by increasing distractibility (scopolamine) (Coull 1998).

Animal models of sensory gating deficits introduced septohippocampal cholinergic regulation in the startle reflex (Flach et al. 1996, Adler et al. 1998). Other transmitter systems important in "gating circuitry" are NMDA-mediated glutamate systems, dopamine-glutamate interactions and GABA (gamma-aminobutyric acid) (Swerdlow 1996). Concerning the pathophysiology of schizophrenia, the α7 nicotinic receptor has

been suggested to play a role as part of an inhibitory pathway in the hippocampus. This inhibitory mechanism may even involve nicotinic stimulation of GABA interneurons, resulting in a decreased response (Leonard et al. 1996, Adler et al. 1998). The interacting cholinergic influence is caused by nicotine enhancing pre and postsynaptic glutamatergic neurotransmission to activate cardiac parasympathetic neurons (Neff et al. 1998). The important role of glutamatergic transmission has been recognized to be related to the therapeutic functions of antipsychotic medications (Ossowska et al. 2000), and evidence of abnormal glutamate metabolism has been shown in schizophrenia (Tsai et al. 1995). However, the underlying pathophysiological mechanisms of glutamatergic abnormalities remain unclear (McCarley et al. 1991, Olney & Farber 1995, Javitt et al. 1996), even though the interaction between the psychophysiological correlates of arousal attention and sensory memory and NMDA receptor function seems evident. It has also been suggested that the hallucinogenic effect of the NMDA receptor antagonist (ketamine) and serotonin-2A (5-HT_{2A}) receptor agonist could be explained by a disturbance in thalamo-cortical gating (Vollenweider & Geyer 2001). There is evidence of GABAergic transmission abnormalities related to both schizophrenia and bipolar disorder. The GABAergic interneuron is considered to be a core component of the corticolimbic circuitry (Benes & Berretta 2001).

Hegerl & Juckel (2000) have brought up a connection between ERP parameters and serotonergic neurotransmission. They present converging arguments from preclinical and clinical studies, which support the hypothesis that the loudness dependence of the auditory evoked N1/P2-response (LDAEP) is regulated by the level of central serotonergic neurotransmission (Hegerl & Juckel 2000, Hegerl et al. 2001, Hegerl et al. 2002). The two N1/P2-subcomponents generated by the primary and secondary auditory cortex are known to be differentially innervated by serotonergic fibres, and can be separated by dipole analysis. A pronounced LDAEP of primary auditory cortices is supposed to reflect low central serotonergic neurotransmission, and vice versa (Hegerl & Juckel 2000, Hegerl et al. 2001, Hegerl et al. 2002). Future studies are, however, needed to assess the potential clinical value of the findings, and to find out if treatment responses to antidepressants and/or lithium can be predicted by the method.

Post mortem peptide measurements of schizophrenic patients' brains have revealed abnormalities in the vasoactive intestinal polypeptide (VIP), cholecystochinin and somatostatin. Of course these peptide findings could be secondary and arise from a previous alteration at the neurotransmitter level, leading to an imbalance in neurotransmitter-neuropeptide interaction. Transmitter findings are complicated by the fact that a single transmitter may have different roles in different brain regions.

3. Aims of the study

I To develop and assess neurophysiological tests for comprehensively evaluating acute psychosis as a psychophysiological state.

II To identify markers of disturbance and imbalance in preconscious autonomic functions in acute psychosis.

III To study the primary sensory representations in acute psychosis.

IV To clarify the alteration in different levels of psychotic forms of attention by electrophysiological correlates of arousal and attention.

V To demonstrate changes in the distribution of stimulus-locked brain activity that are typical of early psychotic disorganization.

4. Subjects and methods

The Information Processing in Acute Psychosis (IPAP) project was established in 1996 with the goals of developing a versatile experimental procedure to study the effects of acute psychosis on different levels of the perceptual system (auditory and visual ERPs), EEG and autonomic nervous system, and bringing the drug-naïve first-episode phase of the illness into focus. The IPAP has been carried out in collaboration with the Departments of Psychiatry and Clinical Neurophysiology of Kuopio University Hospital and the Department of Applied Physics of Kuopio University. The current thesis presents the main results of the initial baseline stage.

4.1. Subjects

The study was conducted on 25 patients (15 females, 10 males; mean age 30 years, range 15-52, SD 12.97), all suffering from an acute psychotic episode and admitted for hospital evaluation for the first time in their lives. All patients had suffered from some kind of prodromal symptoms before the actual overt psychosis, according to the referral and the anamnesis provided by the patients and their relatives (withdrawal, difficulties at school, anxiety, sleeping difficulties), but not from psychotic symptoms. The duration of the prodromal symptoms could not be accurately determined due to discrepancies between the reports. The recordings were made within the first four days in the hospital before any medication was prescribed. The inclusion criteria for our study were firstly that each patient was, for the first time in their lives, disturbed severely enough to be admitted for psychiatric hospital evaluation and, secondly, that patient interviews and hospital records showed that none of the subjects had ever used neuroleptics, antidepressants or anxiolytic drugs, cardiovascular drugs, or any other medication. Two subjects were left-handed. No inquiries were made concerning the subjects' smoking

habits or caffeine intake. Diagnoses were based on information obtained from hospital records and an interview carried out by a trained psychiatrist (M.V.-K.), who was also present during all patient recordings. All interviews included the PANSS (Kay et al. 1987), SCID (for DSMIIIR diagnoses), semistructural scoring and setting the initial diagnoses (see Table 2). Note that the number of subjects in articles I-V varies according to the stage of the ongoing project that they reported.

	Sex	Age	Dg		PANSS	PANSS	PANSS	PANSS
	Male/Female	Years	DSMIII-R		Total	Positive	Negative	Global
Pt1	m	23	298.90	Psychotic disorder	77	17	21	39
Pt2	f	35	295.41	Schizophreniform disorder	106	29	27	50
Pt3	m	19	295.42	Schizophreniform disorder	100	20	34	46
Pt4	f	23	295.43	Schizophreniform disorder	111	26	31	54
Pt5	f	33	296.24	Psychotic depression	99	21	25	53
Pt6	f	15	295.43	Schizophreniform disorder	103	21	35	47
Pt7	f	39	297.10	Delusional disorder	112	26	33	53
Pt8	f	52	297.10	Delusional disorder	100	28	22	50
Pt9	f	16	295.43	Schizophreniform disorder	81	21	22	38
Pt10	f	32	298.90	Psychotic disorder	103	18	26	59
Pt11	f	19	296.44	Mania	109	35	22	52
Pt12	m	20	295.43	Schizophreniform disorder	101	22	32	47
Pt13	f	43	295.30	Schizophrenia, paranoid type	110	31	26	53
Pt14	f	56	297.10	Delusional disorder	104	26	30	48
Pt15	f	16	295.30	Schizophrenia, paranoid type	120	39	22	59
Pt16	m	16	295.70	Schizoaffective disorder	115	24	34	57
Pt17	f	40	295.43	Schizophreniform disorder	99	26	28	45
Pt18	m	32	296.24	Psychotic depression	102	20	28	54
Pt19	m	17	295.43	Schizophreniform disorder	91	23	25	43
Pt20	m	40	297.10	Delusional disorder	96	28	26	42
Pt21	m	44	296.24	Psychotic depression	102	25	28	49
Pt22	f	46	295.43	Schizophreniform disorder	116	35	30	51
Pt23	m	17	295.43	Schizophreniform disorder	83	22	19	42
Pt24	m	19	295.43	Schizophreniform disorder	100	31	23	46
Pt25	f	45	297.10	Delusional disorder	100	34	29	37
	Mean	30.3			101.6	25.92	27.12	48.56

Table 2. Sex, age, DSM-IIIR diagnoses and PANSS scores of the patient group.

The control group consisted of 21 healthy volunteers (16 females, 5 males; mean age 29 years, range 19-46, SD 7.34). There were no significant differences between the ages of the two groups ($p = 0.60$). Two of the control subjects were left-handed. None of the control subjects reported a previous history or family history of mental illness nor any on-going medication.

All subjects provided written informed consent, and the study was approved by the local ethical committee. For underage patients, two consents were provided, one from the patient and another from one of the parents. The electroencephalogram (EEG) is completely non-invasive and is part of the routine diagnostic protocol for first-episode psychotic patients. After the recording, each patient was provided with a handout containing information about the study. It also offered them an opportunity to contact the primary investigator and to prohibit the use of their data for research purposes at any time and without consequences for their treatment, although no patients chose to do this. Three patients wanted to see their own ERPs a couple of weeks after the recording. Although the patients were acutely ill, all recordings were successfully performed, and no serious clinical anxiety reactions were observed in any of the subjects.

4.2. Recording session and stimuli

The two-hour recording arrangement started with electrode fixing and evaluation of the individual hearing level. Two samples of the EEG were then recorded (approximately 90 seconds each) with eyes closed and eyes open, with a fixation point. These were used in calculating a quantitative EEG and evaluating EEG reactivity. Six ERP paradigms were recorded in the main phase of the recording setting, with the EEG, ECG and SSR being continuously recorded during each. The sets were delivered to all subjects in the same order.

In the habituation paradigm, subjects received trains of four tones with a frequency of 800 Hz and an interstimulus interval (ISI) of 1 s. The intertrain interval was 12 s, exceeding the putative duration of echoic memory (Sams et al. 1993). All the tones were

delivered to the right ear of the subject at 55 dB above the individual hearing level. During the first two passive paradigms, subjects watched a silent video throughout the session to keep their attention away from stimuli. They were asked to focus on the plot of the video and ignore the rest of the perceptions.

Next, two sets of oddball paradigms were recorded. The paradigm consisted of 85% standard tones of 800 Hz and 15% random deviant tones of 560 Hz, delivered with an ISI of 1 s. The total number of stimuli was 600. The duration of all auditory stimuli used was 84 ms, including 7-ms rise and fall times, with the stimulus intensity individually set at 60 dB above the hearing level of each subject. During the first set the subjects watched a silent video. During the second set of stimuli the subjects were asked to pay attention to the deviant stimuli and press a button immediately for each of them. Answers were gathered together with reaction times. In the active oddball set 11 human sounds representing novel stimuli were also randomly presented. The subjects were not informed about these before the recording.

In the face recognition paradigm, 489 color photographs (6.5 cm width, 11 cm height) of human faces were used as visual stimuli, with the distance between the subject and the monitor maintained at 1.2 m. The stimuli were divided into four groups representing four emotional categories: neutral, smiling/happy, angry, and frightened. To control and focus their attention, the subjects' task was to press a button when shown all the happy or smiling faces (target stimuli) and to ignore the rest of the stimuli. The duration of each stimulus was 300 ms and the ISI was 1200 ms. Colors, contrasts, luminance, rise/fall times of stimuli and the lighting of the testing room were the same for all subjects throughout the recording session.

In the final two paradigms, each subject performed a standardized digital version of the Wisconsin Card Sorting Test (WCST) (Tien et al. 1996) with two different sets of stimuli in order to evaluate the overall executive functioning of the frontal lobes and working memory (Milner 1963). With the classical set of stimuli, "cards" of 6.5-cm width and 9-cm height representing four different geometric figures, four different colors and the number of figures/card ranging from 1 to 4 were displayed on a computer

screen. The data from the second set is not presented in the current thesis. The subjects' task was to deal the cards according to varying strategies by pressing the button. The duration of each stimulus reflected the time taken by the subject to press the button following the emergence of a new card. On a regular basis, the computer changed the strategy of dealing it required from the subject. Six trials/categories and five changes of strategies was presented to the subject. It also gave a signal voice of positive or negative reward depending on the performance. The hit-rate was calculated as the ratio of correct and wrong answers and reaction times were measured for each pair of stimulus-responses.

4.3. Data acquisition

A 58-channel continuous EEG (Neuroscan Inc.) was recorded using a modified 10-20 system (Regan 1989) electrode cap referred to the right mastoid. However, the common average reference was used for the analysis of the visual paradigm. The skin impedance was below 5 kΩ. The potentials reflecting horizontal and vertical eye movements (4 electrodes), sympathetic skin responses (SSR) and the electrocardiogram (ECG) were also recorded (= 64 channels altogether). All signals were amplified and filtered by a Neuroscan Synamps amplifier (Neuroscan Inc, Sterling, Virginia) with a bandpass of 0.3-50 Hz and digitized continuously at 500 Hz. Trigger pulses from the Neuroscan Stim Audio System P/N 1105 controlling stimuli were stored together with the electrophysiological data.

SSRs were continuously recorded throughout the session with silver chloride (Ag-AgCl) electrodes affixed to the palm and dorsum of the non-dominant hand at the level of the fourth metacarpal bone.

The heart rate was continuously measured during all tests with two Ag-AgCl electrodes attached to the chest of the subjects following the axis of the heart (one electrode near the head and another near the apex of the heart). The sampling rate of the ECG signal was also 500 Hz.

4.4. ERP data analyses

The continuous EEG data were transformed off-line to epochs of -100-900 ms relative to the onset of each tone in stimuli. The eye movement and blink artifacts were removed both automatically (reduction at 75 μV) and based on visual inspection of each individual sweep. The data were averaged and filtered digitally with a low-pass cut-off frequency at 20 Hz (3 dB point of 24 dB/octave roll-off). The number of trials included in the averaged waveforms did not differ between the groups. The maximum peak amplitudes and latencies of each component (P50, N1, MMN, N2b, P3a and P3b in auditive paradigms and P90, N145 and P230 for visual paradigm) were calculated with respect to a 100 ms prestimulus baseline.

In the habituation paradigm a subtraction waveform was defined (the response to the first tone in the habituation train minus the standard response of the passive oddball) as a marker of arousal. To illustrate the local activity, we calculated the regional averages of the N1 amplitudes in three channels frontally (Fp1, Fpz and Fp2), centrally (Cza, Cz and Pza), in the left temporal region (C5a, C5 and T3) and in the right temporal region (C6a, C6 and T4).

In the oddball paradigm, deviant minus standard response subtraction waveforms were calculated. For Article IV, the mean amplitudes were also calculated for latency ranges corresponding to each component with the time window of 60-150 ms for "N1", 100-200 ms for "MMN", 200-250 ms for "N2b", 270-320 ms for "P3a", and 300-350 ms for "P3b". For the statistical model an average of all 58 channels was calculated.

4.4.1. Global field power

The global field power (GFP) was calculated for each waveform (standard, deviant and subtraction waveforms in auditory oddball and visual standard response) from the passive oddball paradigm (Article IV) and for the face-recording (Article V). GFP is a measure defined as the standard deviation across multiple channels as a function of time and the intention of it is to quantify the instantaneous global activity across the spatial

potential field sampled over the scalp. We utilized the latencies of maximum peaks (negative or positive) of GFP to calculate cortically constrained current source density maps.

4.4.2. SSR data analyses

For SSR the data was transformed into epochs of -1000 – 6000 ms with respect to the stimulus onset. No artifact removal or filtering was performed. In Article III the group average waveforms of SSR for the first habituation trial (for the first train of four tones) and for the last trial (*i.e.* 29th train) were presented. In Article I the SSRs for the novel stimuli within the active oddball paradigm were taken under closer consideration. Both grand averages and single trial individual SSRs were presented. The group-specific waveform characteristics were further demonstrated by the blind rating of SSRs into patient and normal subject categories by volunteer evaluators. The strength of agreement for individual rater/reality situations and between raters (20 physicians and hospital laboratory staff) was presented.

4.5. HRV data analyses

For HRV evaluation, three ERP paradigms were used on the basis of the putative mental load. The passive oddball paradigm was considered to be easiest for the subjects (PASSIVE), the active oddball paradigm was considered to require moderate mental effort (LIGHT LOAD) and the WCST was considered to be the most demanding (HEAVY LOAD).

All data were manually checked to eliminate any potential ectopic beats, arrhythmic events, missing data, and noise effects, which would alter the PSD estimate for HRV. At this point, the recordings from one patient were excluded from further analyses because of ventricular extrasystolia.

Discrete event series (R_iR_{i-1} intervals as a function of R_i occurrence times) were constructed by an adaptive QRS detector algorithm. The low-frequency trend in the series was extracted by fitting a second order polynomial. In order to recover an evenly sampled signal from the irregularly sampled event series, a cubic interpolation was applied. From this evenly spaced signal, a commonly used nonparametric power spectrum density estimation, based on fast Fourier transformation, was carried out.

The results of the HRV measurements were presented following the division of methods recommended by the Task Force of the European Society and North American Society of Pacing and Electrophysiology (1996a, 1996b). They are presented in detail in Article II and in the summary in next chapter of this thesis (*Summary of results*).

4.6. Statistics

Statistical comparisons between the two groups were performed by using the general linear model for repeated measures (SPSS for Windows, versions 9.0 and 10.0). Stimulus types and channels were within subject factors. The amplitudes and latencies were tested in separate models. In all models, the between-subject factor was the group (patient or control). Age, sex and education in years were tested as covariates in all models. Age was the only variable that showed significant interaction with the electrophysiological and behavioral data. The models employed Greenhouse-Geisser adjustments for the degrees of freedom to correct for the violations of the sphericity assumption when appropriate. The post-hoc testing of significant results was performed using the independent samples *t*-test. The level of significance was set at $p < 0.050$. Correlations between neurophysiological parameters and PANSS scores were calculated using Spearman correlation matrix (except in Article III, where the Pearson matrix was used.). For the data that did not follow a normal distribution, the non-parametric Mann-Whitney *u*-test was applied. Additional models were used to study the influence of diagnosis on the neurophysiological findings. For this purpose, two preliminary diagnostic sub-groups were entered into a separate model as a between-subject factor

(schizophrenia *vs.* non-schizophrenia groups). In HRV and oddball analyses the performance in the P300 target detection task and WCST and reaction times were also tested as covariates in the statistical models. They had no significant interactions with the neurophysiological results.

4.7. Visualization of EEG

Two commercially available complementary software packages were used for spatiotemporal analysis of scalp-recorded electrical fields (Curry and BESA) and visualization of the grand average data. The maps display an estimate of the areas of maximum activation or activity distribution differences in the brain at the group level.

4.7.1. Curry

In Articles III, IV and V, Curry 4.0 (Neuroscan Inc., Sterling, Virginia) was used to compute the current source density maps, which were calculated with the minimum norm regularization. The realistic head conductor model was created from 3D-magnetic resonance images (one control person), and the same head model was used for both groups. The electrode locations were digitized with a 3D navigator Polhemus (Colchester, Vermont) and aligned with MR images.

4.7.2. BESA

For the equivalent current dipole analysis (BESA (Scherg 1994)), we used group averaged data from patients and control subjects, and a window of 0-400 ms after a face stimulus. Principal component analysis (PCA) was first performed on the data to estimate the optimal number of dipoles. The dipole model was developed with the orthogonal dipole strategy. Each dipole was freely fitted for location and orientation while aiming for the smallest possible residual variance. The aim was to find the least,

but still sufficient and physiologically feasible, number of dipoles to allow temporal separation of the major active sources at 0-400 ms poststimulus. Finally, the obtained location coordinates for each dipole were transformed into the coordinates of a stereotaxic brain atlas (Talairach & Tournoux 1988), and the approximate cerebral structures implicated by the dipoles were identified.

5. Summary of results

5.1. Behavioral measurements

As a behavioral control, the subjects' performance of the tasks (See *Recording session and stimuli* section) as well as the reaction times were recorded.

In active auditory oddball paradigm, identification of the targets and the reaction times of the answers were measured. The patients made four times more mistakes than the controls ($F = 11.31$; $df = 1$; $p = 0.002$). On average they made 2.0 incorrect reactions for standard tones, while controls reacted only 0.5 times. They also missed 3.9 target tones, whereas controls only missed 0.8 targets. Interestingly, however, reaction times did not differ between the groups ($p = 0.57$).

In the face recognition task, the patients made significantly more false reactions to non-target faces ($p = 0.031$) and missed more smiling faces ($p = 0.016$) than did the control group. The patients' reaction times were also significantly slower ($p = 0.035$) than those of the controls in the face task.

In the classical patterns digital version of the Wisconsin card sorting test (WCST), the patient group made more mistakes than control subjects (hit-rate: 0.71 *vs.* 0.57 in controls, $p = 0.22$, group average was 20% higher) and the overall reaction time was significantly slower in patients than healthy controls (5.01 *vs.* 2.00 seconds in controls; $Z = -3.07$, $p = 0.001$).

5.2. Sympathetic skin responses are poorly time-organized in acute psychosis (Article I)

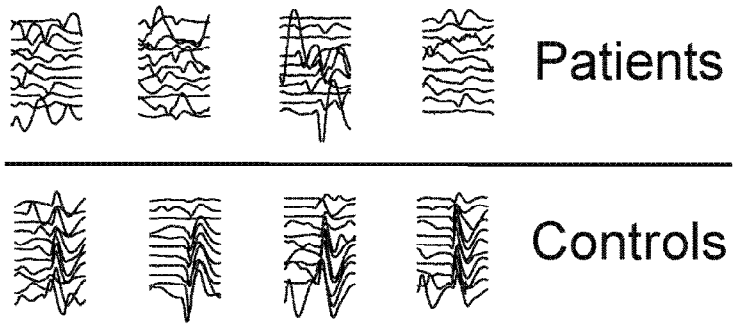


Figure 2. Three examples of typical response panels (patients above, controls below). The lowest waveform in a panel is the SSR for the first novel tone in the paradigm and the uppermost for the 11th novel stimulus. Note the clear time-locking in each panel of random response patterns for controls and patients.

Healthy control subjects showed a stable time-locked (1300-1800 ms) set of responses to novel auditory stimuli, whereas psychotic patients displayed no time-locked pattern of responses. Group-averaging showed the typical hyporesponsiveness in patients (Öhman 1981, Dawson et al. 1992). However, the single trial data revealed that all subjects responded to stimuli, but considerable jitter of these single trial responses diminished the averaged responses of most psychotic subjects, whereas the solid SSR pattern of control subjects was strengthened by averaging. Examples of typical response patterns are shown in Figure 2.

Subject	Real Group	Rater 2	Rater 12	Rater 14	Rater 19	Rater 20	Neg ratings True	Neg ratings False	Pos ratings True	Pos ratings False
1	**Ctr**	Pat	Pat	Pat	Ctr	Pat		1		4
2	**Pat**	Pat	Pat	Pat	Ctr	Pat	1		4	
3	**Ctr**	Ctr	Ctr	Pat	Ctr	Ctr	4			1
4	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
5	**Ctr**	Ctr	Ctr	Ctr	Ctr	Pat	4			1
6	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
7	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
8	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
9	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
10	**Ctr**	Pat	Pat	Pat	Ctr	Pat	1			4
11	**Ctr**	Pat	Pat	Pat	Pat	Pat	0			5
12	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
13	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
14	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
15	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
16	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
17	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
18	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
19	**Ctr**	Ctr	Pat	Pat	Ctr	Pat	2			3
20	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
21	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
22	**Pat**	Pat	Pat	Pat	Ctr	Pat		1	4	
23	**Ctr**	Pat	Ctr	Pat	Ctr	Pat	2			3
24	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
25	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
26	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
27	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	
28	**Ctr**	Ctr	Pat	Pat	Pat	Pat	1			4
29	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
30	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
31	**Ctr**	Ctr	Ctr	Ctr	Ctr	Ctr	5			0
32	**Pat**	Pat	Pat	Pat	Pat	Pat		0	5	

Table 3. The ratings of the top five raters are presented. All the raters (Code numbers 2, 12, 14, 19 and 20) were professionals in either EEG or biosignal analysis (university physicists and clinical neurophysiologists). The total number of response panels rated was 32 (13 patients and 19 controls). In the table on the right side the numbers of false/true positive and false/true negative ratings are presented.

Twenty evaluators were recruited to rate the response patterns in psychotic and normal categories after having seen examples of the typical response trend of a patient and a control (Figure 2). The sensitivity and specificity of the ratings are presented for all

subjects and for an evaluator subgroup consisting of top five raters. 10 doctors and medical physicists familiar with signal processing, clearly profited from their experience, and achieved higher specificity and sensitivity scores than the rest of the raters. The average strength of agreement in this subgroup was almost perfect (Landis & Koch 1977), and the overall agreement between the raters was moderate. The top five raters in the subgroup reached 100% sensitivity and were able to correctly identify all the patients, with false positive score of 24%, and the adjusted κ was 0.92 (Table 3).

5.3. Psychotic patients show less short-term heart rate reactivity than healthy controls (Article II)

Visual analysis of the raw HRV data confirmed in 13 of the 20 healthy controls a clear negative correlation between HRV and the task requirements, whereas no visually detectable changes in HRV were observed in any of the psychotic patients.

Mathematical analysis of the HRV data included time-domain methods, statistical methods, geometric methods and frequency domain analyses (1996a, 1996b). Table 4 presents the main results of these analyses. The patients had higher heart rate than the controls, and their short term variation of the HR was decreased (measured by RMSSD and pNN50). Patients HF power was decreased. The mean RR and mean HRV correlated with age of the subjects as known previously in the HRV literature. There were no significant interactions with sex or education.

The task-dependent HRV changes were also mathematically evaluated and the patients' poor reactivity was confirmed. Their HRV parameters remained unchanged across all three conditions, whereas the controls exhibited adaptation of HRV in task connected strain. There were no significant differences between the HRV findings and the diagnostic subgroups (schizophrenia *vs.* non-schizophrenia group).

The PANSS scores for apathy, social withdrawal and invert withdrawal were correlated with several HRV parameters and HR reactivity (see II, Table 3). The change in HF power (increase in vagal influence affecting the sympathovagal balance) between the tasks correlated positively with positive symptoms, the amplitude of HF power correlated negatively with global psychopathology index (implying that the increase in global psychopathology was related to decrement in HF power). Short term variation of HRV (measured as RMSSD and pNN50) correlated negatively with the hostility. Several negative symptoms had a negative correlation with HR, that is to say the higher heart rate, the lower ranking in negative scores.

	Controls			Patients			
HR	"MMN"	"P300"	"WCST"	"MMN"	"P300"	"WCST"	
Variable	**Passive**	**Light load**	**Heavy load**	**Passive**	**Light load**	**Heavy load**	**Units**
$\boxed{RR}$	816±112	802±109	765±137	759±111	752±111	732±116	(ms)
σRR	41±16	39±13	41±16	36±15	33±13	34±13	(ms)
$\boxed{\overline{HR}}$	75.0±9.9	76.3±10.1	81.0±13.7	80.9±11.4	81.6±12.1	84.1±12.7	(1/min)
σRR	3.8±1.2	3.6±0.9	4.3±1.7	3.9±1.7	3.5±1.2	3.9±1.7	(1/min)
RMSSD	38.8±18.8	35.8±16.5	31.5±17.8	24.4±9.9	24.2±11.4	23.9±11.2	(ms)
pNN50	18.8±16.9	18.2±17.2	12.4±14.4	6.1±6.5	6.6±9.0	6.5±9.0	(%)
HRVTI	70.5±21.3	69.8±19.3	66.5±17.1	60.3±16.9	62.8±21.6	58.9±18.0	(ms)
TINN	186±63	174±54	179±65	156±54	157±57	149±53	(ms)
LF power	45.3±19.8	38.5±18.2	49.0±15.5	52.4±15.4	45.9±18.5	46.5±15.6	(%)
HF power	40.2±22.8	40.7±21.8	33.1±19.5	28.5±17.3	29.1±16.9	28.8±18.2	(%)

Table 4. Group averages and standard deviations of obtained variables. RR is the mean RR interval, σ_{RR} is the standard deviation of RR intervals, $\overline{HR}$ is the mean heart rate, σ_{HR} is the standard deviation of HR signal, RMSSD is the square root of the mean squared differences of successive RR intervals, pNN50 is the relative number of successive adjacent RR intervals with a difference of greater than 50 ms, HRV_{TI} (HRV triangular index) is the integral of the RR interval density function divided by the maximum, TINN is the baseline width of the density function, and LF power and HF power are the low and high frequency band powers of the PSD.

In summary, even though the patients exhibited a higher heart rate across all three conditions, the only significant differences between the groups concerned large short-term variation in HRV (measured as RMSSD and pNN50) and HF power. The patients had a significantly lower RMSSD (the square root of the mean squared differences of successive RR intervals) and pNN50 (the relative amount of successive adjacent RR intervals with difference greater than 50 ms) and high frequency power (HF).

5.4. The N1 enhancement in frontal channels in acute psychosis – hyperarousal in orienting networks of the brain (Article III)

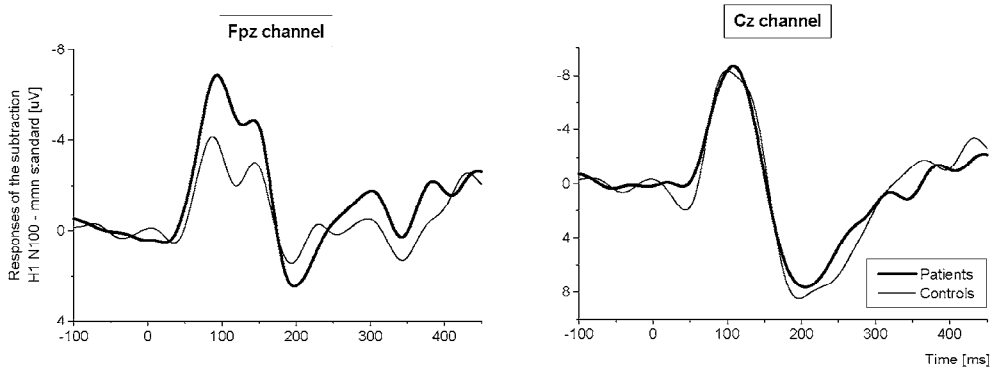


Figure 3. The arousal of patients (thick line) and controls (thin line) measured as the response to the first tone in a train minus the response to a standard tone at the Fpz channel (left) and the Cz channel (right). The difference between groups is evident in frontal leads.

In frontal channels, the amplitudes of the auditory N1 evoked by the habituation trains of four tones (and the first tone in particular) were significantly higher in patients when compared with controls (the mean amplitude in channel Fpz -11.2 μV, SD 5.0 *vs.* -8.3 μV, SD 2.8; $F = 4.84$, $p = 0.037$). Centrally, the responses did not differ between the patients and controls (in Cz 15.8 μV, SD 6.1 *vs.* -14.9 μV, SD 4.5; $F = 1.58$, $p = 0.22$) (see Figure 3); nor were there any amplitude differences between the left and right temporal regions. However, there were differences between patients and controls concerning the spatiotemporal distribution of the brain activity (Article III, Figure 2).

The degree of habituation of the N1 amplitude was similar in both groups (group × tone interaction frontally: $F = 1.36$, $p = 0.26$; and centrally: $F = 1.44$, $p = 0.25$). Thus, the N1 amplitudes remained significantly larger in patients than in controls throughout the train of tones.

The current source density maps illustrate the altered, frontally emphasized cortical distribution of auditory arousal activity in psychosis, also demonstrated in the subtraction waveform data (response to the first tone in a train minus oddball standard response) (see III, Figures 2 and 3).

In sympathetic skin responses the patients showed lower amplitudes to the arousing tone as well as an impaired habituation trend. There were no significant correlations between the PANSS scores and N1 amplitudes, except a negative correlation between the anxiety score and several of the tested 58 N1 amplitudes and a probably less relevant positive correlation between the positive sign of grandiosity and N1 amplitudes.

5.5. Alteration in auditory processing in acute psychosis (Article IV)

The patients exhibited a trend of more negative amplitudes than controls concerning brain activity within all five time windows (corresponding the latency ranges of "N1",

"MMN", "N2b", "P3a" and "P3b" components; see IV, Table 2), revealed by both GFP maximum peaks within the time window and mean amplitudes of all 58 channels for each time window in all standard and deviant responses as well as the subtraction. However, the differences between the groups were only significant in attention-dependent later processing (time window of "N2b", "P3a" and "P3b").

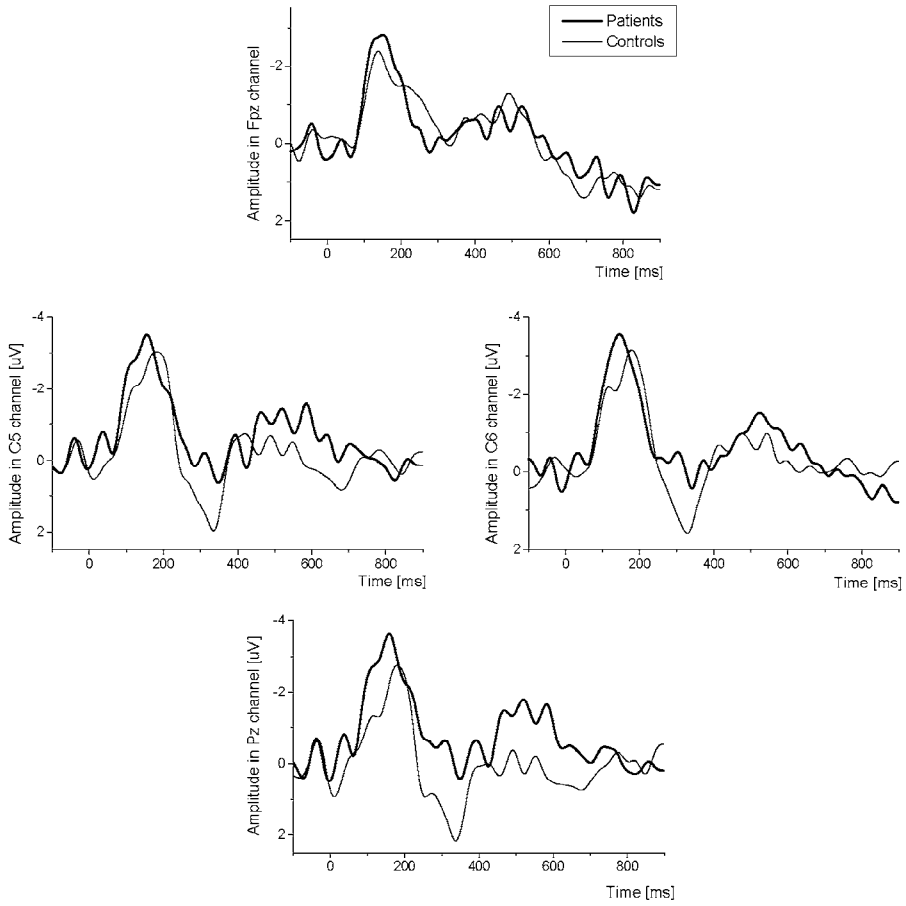


Figure 4. The deviant - standard subtraction waveforms are presented for four channels (Fpz above, C5 left, C6 right and Pz below) for patients (thick line) and controls (thin line). Note the hypernegativity during early processing and the decreased amplitudes within the latency range of the later time windows.

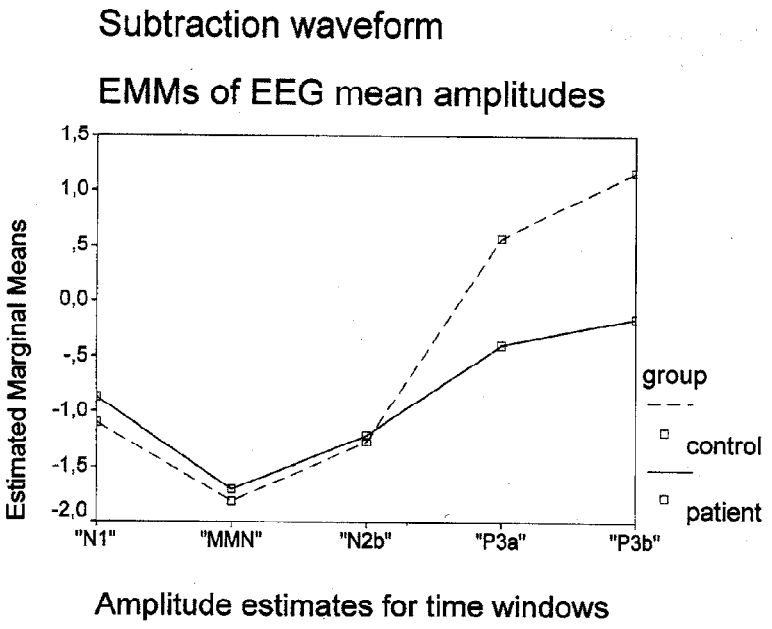


Figure 5. Estimated marginal means of the average mean amplitudes of the subtraction waveforms. (See also IV, Figure 2, where the deviant and standard response EMMs are presented separately, revealing the underlying changes in measured responses).

None of the latencies of the GFP maxima differed between the groups. The patients' hypenegativity was clearly seen in deviant responses (See IV, Figure 1 and Figure 2). The standard responses revealed the amolitude difference between the groups on in later windows. The age had a significant effect on GFP values. The GFP amplitudes decreased with age. There were no significant interactions with GFP maxima and sex or education of the subjects.

The patients displayed more negative EEG mean amplitudes than controls within all five time windows of deviant responses. The significant main effect was due to differences in later processing (N2b, P3a and P3b). The age had also here a significant effect on EEG amplitude, but sex and education did not have effects on EEG. In subtraction waveforms (See Figure 4) the difference between groups was significant only at the latency range of P3a and P3b. The earlier and increased MMN amplitude (negative peak in subtraction waveform at about 200 ms poststimulus) was seen in several channels, but this interesting group difference was not significant. In MNE visualization, the controls exhibited the well-defined bitemporal and a clear frontal activity, whereas the patients showed weak, poorly organized activity bitemporally, but no frontal activation (See IV, Figure 3).

5.6. Enhanced face-sensitive visual ERP component in acute psychosis (Article V)

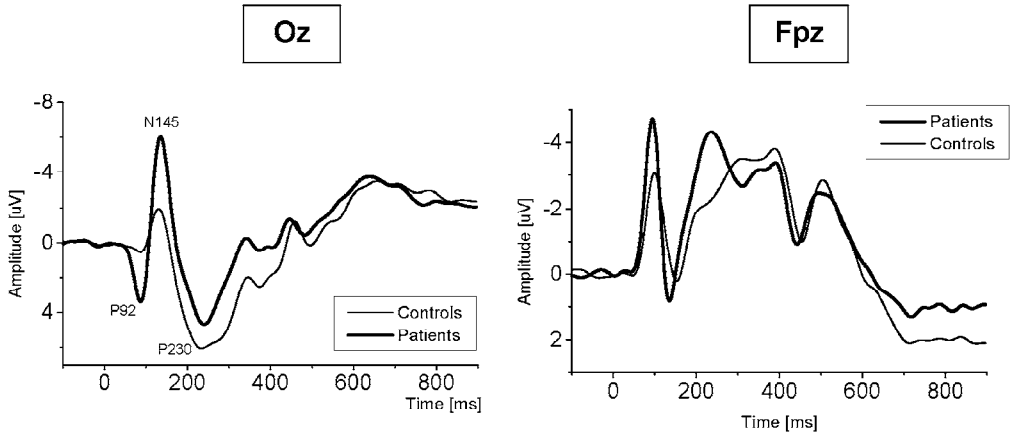


Figure 6. Visual ERPs of patients (thick line) and controls (thin line) for standard faces in the occipital channel (Oz, left) and prefrontally (Fpz, right). Note the P92, N145 and P230 component locations marked in the Oz waveform.

The amplitude of the 145 ms ERP component following the non-target face stimuli was of significantly higher ($-2.97 < Z < -1.95$; $0.050 < p < 0.000$) amplitude in patients than in controls in six channels out of the seven included in the statistical analysis (*e.g.* FPZ: $Z = -1.32$; $p = 0.19$). The mean GFP waveform further confirms the finding by showing an extra peak of activity in patients that is not seen in controls at around 145 ms (see V, Figure 1b). The N145 peak reached its maximum amplitude in CB channels in the temporo-occipital junction for both groups, where the difference between the groups in N145 amplitudes also reached its maximum (Figure 7 presents the scatter of the responses in both groups). The latencies of visual ERPs did not differ between the groups (see V, Table 2.). Importantly, the maximum amplitudes during the earliest visual cortical responses at 92 ms did not differ between the groups. Thus, the difference between the patients and controls only became evident concerning later, stimulus specific components of the responses.

In patients, the amplitude enhancement was also seen in the 230 ms component (CB1: $Z = -2.20$; $p = 0.027$; O1: $Z = -2.36$; $p = 0.018$), but in other channels there were no significant differences between the groups ($-1.79 < Z < -1.16$; $0.08 < p < 0.26$). Moreover, the latency of the P230 component in the central Cz channel was significantly delayed in patients ($Z = -3.21$; $p = 0.001$) (see V, Table 2).

Minimum norm estimates and the initial single dipole modeling showed significant differences between patients and controls in the temporal and spatial distribution of the activity around 145-230 ms (see V, Figure 2). Controls showed weak activity in visual cortical areas and the single equivalent dipolar source lay superficially on the inferior occipital cortex (see V, Figure 2). In patients, more prominent activity could be seen in several extrastriatal areas of the visual cortex. The single equivalent dipole was located in the midline over the parieto-occipital junction, possibly reflecting electrical activation of bilateral fusiform gyri as well as other nearby cortical sources (see V, Figure 2).

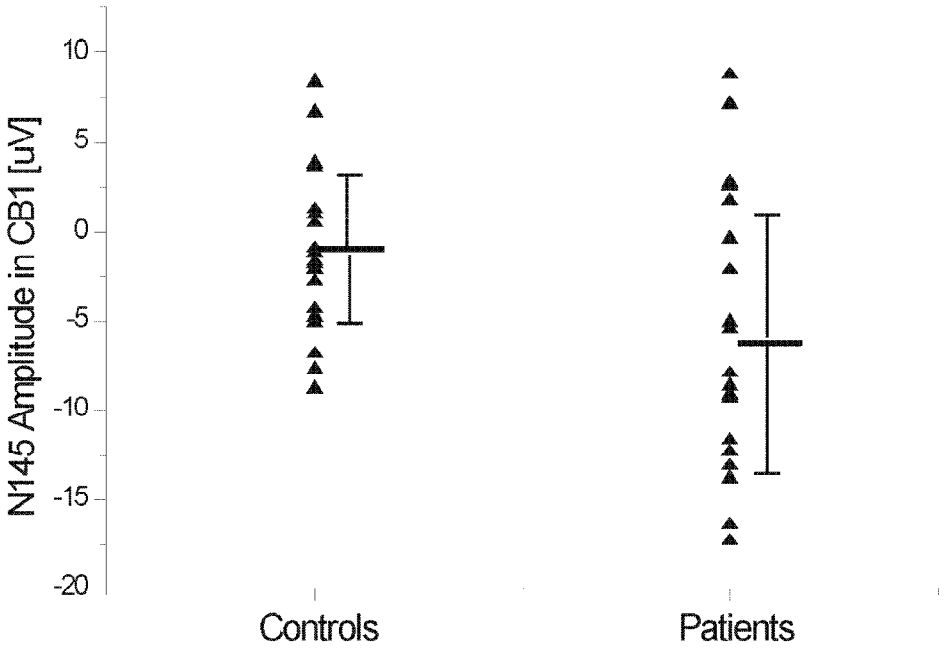


Figure 7. The scatters of N145 (in CB1 channel) amplitudes of both groups (controls left, patients right). Means with +/- 1 SD are presented on the right.

Multiple dipole models were independently calculated for patients and controls, and are presented in V, Figure 3. Both sets of data could be satisfactorily explained by 5 dipolar sources. The source potentials described temporal activation of each source throughout the analyzed 400 ms (see V, Figure 3). Remarkably, in patients the strength of dipole 1 reached up to 20 μVeff compared to 2 μVeff in controls. The location and orientation of dipole 1 also differed strikingly between the groups. In patients, it lay in deep midline brain structures around the ventriculus quartus, and may have even been cerebellar, whereas in controls it was located in the visual cortex. The differences between the groups in dipoles 2, 3, 4 and 5 were negligible. The overall residual variances of both of

the models were below 5% within the time window.

There were no significant correlations between the amplitudes or latencies of the three peaks in the seven channels and the PANSS scores, except for the negative correlation between the N145 amplitude in CB1 and CB2 channels and the anxiety score of the Global Psychopathology Index (Spearman correlation -0.375; $p = 0.035$). There were no significant interactions with ERP parameters and sex or educational level of the subjects. However, age of the subject correlated with P92 amplitudes.

6. Discussion

The aim of present study was to use a multidimensional approach to evaluate acute psychosis as a psychophysiological state. We developed a multilevel test battery to identify typical markers of an early psychotic break-down in autonomic functions and at different stages of sensory perception. We extensively studied acutely ill drug-naïve first-episode patients and obtained a versatile picture of their psychophysiological state. The main finding was that in acute psychosis several early ERP component amplitudes in both auditory and visual paradigms were enhanced. This was contrary to previous literature findings reporting wide amplitude attenuation in chronic medicated patients. In addition, signs of decreased short-term variation in heart rate variability, lack of time-organization of sympathetic skin responses, and aberrant topography in ERP distribution were found. The finding of diminished attention-dependent late cognitive components was replicated in our study, confirming previously published reports.

The current study provided a picture of acute psychosis as a psychophysiological state. Acutely psychotic individuals showed alterations at several levels of information processing when compared to healthy controls. There were disturbances in the timing and flexibility of the autonomic nervous system responses in psychosis. In addition, the early sensory ERPs were increased in amplitude, while hypoactivity was detected in later processing in patients. Our results clearly support the theory of psychosis as a profound and holistic state, which should not to be underestimated by reductionism. This being the case, the following discussion offers a few points of view based on our findings and outlining the current status of the field and the direction of future studies, rather than providing any definite solutions to the problem of psychotic breakdown.

6.1. Motivation to study first-episode psychosis – determination of the concept of psychotic illnesses defined by scientific methods and findings

During recent years several theories have been introduced in an effort to clarify the etiology and pathophysiology of psychotic illnesses. The neurodevelopmental hypotheses have attracted considerable criticism and a number of different "unitary" models have emerged. The majority of these models share a dimensional type of diagnostic thinking, which is suitable for current research methods. It may not be sensible to seek a "schizophrenia gene", but it seems more relevant to try to identify vulnerability genes for sensory gating deficits or alterations in smooth pursuit eye movements, both common findings in schizophrenia. This is one example of the current trend of combining different methodologies in an effort to obtain new approaches and insights. Our results support the view that psychophysiological measures may provide new candidate tools for integrative approaches.

The multidimensional phenotype of psychoses (schizophrenia in particular) has been a difficult problem for researchers trying to find distinct subtyping for their studies. Even though classifications have been developed for more than a century, the heterogeneity of the diseases has still led to a mixture of several subtypes in a substantial number of cases (Liddle 1999). The classical subtypes of Bleuler and the DSM diagnostic categories are typical examples of a categorical type of classification. Although there are still active groups against unitary models supporting categorical subtyping (Kendler et al. 1998, Kendler & Walsh 1998, Kendler 1999), even some of the classical properties of categorization have been dimensionalized, as for instance the Schneiderian first-rank symptoms have been shown to have heritability independent of schizophrenia (Cardno et al. 2002). However, the following three examples are the most plausible basis for psychophysiological studies.

First, Crow has presented a dimensional theory of positive and negative symptom pools (Crow 1980, Crow 1998, Liddle 1999). He argues that there are no disease entities, but only a continuum of variation. In his model, the psychoses represent an

extreme of hemispheric lateralization, making the evolution of language possible.

Second, Csernansky & Bardgett (1998) have demonstrated a relationship between the increasing damage to neuronal circuits and clinical phenomenology of psychotic illnesses. They relate this to the individual capacity to respond to antipsychotic drugs, and suggest a physiological continuum in the relationship and the limbic-cortical neuropathology (Csernansky & Bardgett 1998).

Third, Andreasen's unitary model, termed *cognitive dysmetria*, is an attempt at a more abstract cognitive model, not just a symptom based one. It also provides a heuristic theoretical framework for etiology, pathophysiology and treatment, including all these elements on the CCTCC (cortico-cerebellar-thalamic-cortical-circuitry) (Andreasen 1999).

In factor analysis studies, measures of psychosis have not differentiated schizophrenia from other forms of psychopathology, leading to dimensional thinking based on the factor analysis (Stefanis et al. 2002). According to these studies, psychosis is not specific to schizophrenia or even to psychiatric disorders as it is often seen, for example, in neurological or trauma patients. In a three dimension model of psychotic experiences with positive, negative and depressive factors, there was a certain distribution even in the general population. The authors suggest that the depressive pool is an integral part of the psychotic continuum at the subclinical level (Stefanis et al. 2002).

The evidence for a common neuropathology in major depression, bipolar disorder and schizophrenia has led to the development of the vulnerability-stress model in an effort to explain findings by glucocorticoid-related suppression of activity and providing complementary elements for neurodegenerative or neurodevelopmental hypotheses (Cotter & Pariante 2002). The vulnerability-stress model is also associated with alterations in the autonomic nervous system in psychotic illnesses.

Perhaps the most integrated of recent theoretical models of psychosis is the "multiple hit" hypothesis, where an accumulation of genetic and environmental risk factors (or lack of environmental protective factors) may lead to premorbid manifestations, and

depending on later additional insults this early-life situation may remain stable throughout life, evolve into less severe mental disorders or lead to a psychotic illness (Rabinowitz et al. 2002). These "hits" may include infectious diseases in mothers during pregnancy, birth complications or accidents during childhood.

One important advantage of dimensional thinking is that the first-episode patient's status has been emphasized. Efficient recognition of the early signs of psychosis and optimal management result in a better outcome (McGorry 2002). Old concepts, such as *schizotaxia*, have been reformulated and put to use to define risk-groups for preventive interventions (Tsuang et al. 2000b), or as with the *cycloid psychoses* (motility, confusion and anxiety-happiness psychoses), to complete the diagnostics of non-schizophrenia-like psychoses (Jabs et al. 2002). The effectiveness of lower doses of antipsychotic medication has been particularly demonstrated for first-episode psychoses, and it has been shown that the first treatment intervention for the initial episode of illness is a critical opportunity to influence the long-term course of the illness (Drake et al. 2000, Jarskog et al. 2000).

Early diagnostics of overt psychosis has also raised the question of prodromal signs, since poor premorbid functioning before the onset of psychosis has been associated with more severe symptoms and cognitive manifestations of illness (Rabinowitz et al. 2002). There is preliminary evidence that structured interviews to identify prodromal signs provide promising interrater reliability and predictive validity (Miller et al. 2002). This is an example of the clinical benefits derived from the progress in dimensional thinking.

It is clear that contemporary research on the mechanisms of psychosis can help to understand the illness on multiple levels simultaneously combining the data from several disciplines to create interactive models of the disorder (Andreasen 1996). The goal of dimensional thinking is this integration of models, which we also attempted in our study.

6.2. Technical discussion

6.2.1. Observations of recording sessions

All recordings in the present study were carried out in a silent room at the Department of Clinical Neurophysiology, Kuopio University Hospital. I met each patient before the recording at the psychiatric ward and made the initial diagnostic evaluation of whether there were sufficient signs of reality-testing disturbance to include the patient in the psychosis subgroup. We travelled together to the testing site and I was present during the electrode placement. Most of the patients (and healthy controls) considered the fixing unpleasant because of the scratching carried out by two nurses simultaneously to check all channels as quickly as possible and guarantee an adequate impedance level. I tried to maintain a supportive atmosphere and provide information to the patients about the registration, as well as rapidly respond to their concerns.

Three patients were excluded before entering the laboratory, one because of suspected drug abuse and two because of a potential risk of violent acts. Contrary to my expectations, none of the patients had to discontinue the session, even if it took 2 to 3 hours. One patient interrupted the recording to eat a snack before continuing and another to go to the restroom. Several subjects drank water and stretched between recordings. I was present during all recordings and gave instructions to each patient and brought the patients back to the psychiatric ward after the recording. Supportive medication (bentzodiazepins) was at hand in case of severe anxiety or emergency, but it was not needed.

Most of the structural interviews were carried out the day after the recording, which offered a good starting point for conversation, since the majority of the patients were very interested in the methods used and their own performance as well as the potential results. One patient wanted to have a written statement of her EEG and ERP findings and two others inquired about their results by phone. I was surprised by the enthusiasm of the patients in trying to achieve the best possible performance, although they were suffering from severe symptoms. Interestingly, none of the patients mentioned that the

electrodes were uncomfortable as the recording continued, not even when asked if they had a headache, but all healthy controls complained of this in the final stage of the recording. The fact that we succeeded in preventing dropouts was an achievement thanks to the high professional quality of assisting personnel and the amazing cooperativeness of the patients.

6.2.2. Subjects – symptom-related effects

One of the aims of current study was to develop psychophysiological methods applicable in psychiatric disorders. Psychosis represents a psychiatric emergency, and though a complex phenomenon, it is often clinically rather easy to identify. It is among the most severe psychiatric illnesses and is often accompanied by traumatic elements. It is therefore a natural target when developing tools for better psychiatric diagnostics, treatment evaluation, rehabilitation and screening. Medication has a well-studied effect on psychophysiological responses and biosignals, but there was a lack of studies on never-medicated patients in the late 1990s, legitimating the use of drug-naïve patients. Even though acutely ill patients were more difficult to record, it was necessary to schedule the study to coincide with acute symptoms in order to obtain state-specific data. State-dependent changes in, for example, deviance detection (MMN) have recently been reported in schizophrenia spectrum disorders, which makes the current approach particularly relevant (Shinozaki et al. 2002). When medication issues and acute symptomatology took priority over other matters, incomplete attention was directed, for instance, towards differential diagnostics.

Several antipsychotic drugs are known to have significant effects on the autonomic nervous system (Dawson & Nuechterlein 1984, Dawson et al. 1992, Dawson et al. 1994, Agelink et al. 1998, Öhman et al. 2000) and the EEG (Milstein et al. 1984, Lifshitz et al. 1987, Eikmeier et al. 1991). Most previous studies have focused on medicated patients. Few reports have examined patients who are drug-free at the time of recording (Fowles et al. 1970, Catts et al. 1995, Michie 2001), although previously medicated (Zahn et al. 1979, Zahn et al. 1981a, Zahn et al. 1981b, Shinozaki et al. 2002). Our findings thus

reveal disturbances in ANS and EEG regulation that are related to the psychotic state *per se* and are not secondary consequences of chronicity or any treatment modality.

The relatively small number of patients in the present study reflected the rigorous inclusion criteria. Some patients were excluded because of previous medication or drug abuse, or because of aggression or violence, which would have prevented reliable interindividual comparisons. In addition, there may be gender-specific EEG differences, which were not assessed in the report on the habituation paradigm (III), as only female patients were included in that article (Kline et al. 1999).

Our patients were acutely ill, preventing the lengthening of the total recording time, and not all interesting variations could thus be included in the session. No recording had to be discontinued because of anxiety or for any other reasons related to the state of the patients, and a negative correlation was observed between ERP markers and PANSS anxiety scores (II, III, IV, V).

HRV findings were related to several PANSS scores, particularly to apathy and withdrawal scores of both negative signs and global psychopathology. It can be speculated that these negative signs influenced cognitive performance and thereby affected HRV. However, clinical observation showed that all subjects coped with the tasks, although the patients attained lower hit-rates and made more mistakes than the controls. Moreover, none of the performance parameters had a significant effect on HRV in statistical GLM models, or in the correlation matrix, where the only significant correlations were between age and the reaction times (as expected from previous findings reported in the literature), and with performance parameters and diagnosis. There were also separate significant correlations between several ERP and HRV parameters and PANSS scores (*e.g.* suspiciousness, delusions and motor retardation), but our results do not support the previous conclusion that changes in acute psychosis could be specific to any symptom cluster (Brekke et al. 1995). In the habituation paradigm, the only significant correlation between auditory N1 and PANSS scores was the negative correlation between anxiety and the ERP amplitude.

In an effort to study the potential differences between the schizophrenia and non-schizophrenia types of psychotic illness, subgrouping was used in the statistical analysis. There were no significant differences in any biosignal parameters between schizophrenia and non-schizophrenia subgroups. The subgroups were rather small, making our effort somewhat artificial. As noted, more data would be needed to extend these psychophysiological findings over pathophysiological differential diagnostics.

6.2.3. Methodological issues

In general, all recordings were performed technically very well. Low impedances were obtained, which guaranteed a good quality signal. The patients exhibited more eye movement artifacts than controls, and for all reports the artifact reduction was carried out both automatically (+/- 75 μV treshold) and based on visual inspection. In the most severe cases, electrical correction of eye movements was used.

6.2.3.1. Sympathetic skin responses

Single trial SSRs provide direct visual information on individual responses and give an opportunity to qualitatively characterize different patterns of SSRs. In averaged SSRs, the individual response characteristics are lost, which may be a significant methodological drawback. In our data, the patient group with low SSR amplitudes (probably ranked as non-responders in earlier studies) also exhibited visually detectable temporal disorganization of responses. The higher sensitivity of the SSR test used in this study, compared to the SCR, promotes the observation of the weakest and the more random responses.

The human sounds used as novel stimuli were attention-capturing enough to induce novelty detection and SSR, but satisfactory co-operation of the subjects was nevertheless maintained during the experiment because no fear or anxiety reactions were provoked. This is crucial when recording responses in drug-naïve acutely ill patients.

The sensitivity and specificity of the visual sorting test may be further improved by training of the raters. Pattern recognition algorithms may be applied as a way to further develop the clinical value of SSR recording in acute psychotic states.

6.2.3.2. Heart rate variability

The electrocardiogram recordings were succesfully carried out. The data of one patient was excluded because of ventricular extrasystolia. The quality of the heart rate sample chosen for analysis of the parameters is important, since potential slow-wave fluctuations in the raw data can lead to artifacts that prevent reliable estimation of heart rate variability within a sample. This problem was resolved by choosing each sample visually and by using a second order polynomial fitting to remove the slow potentials. The error in RR intervals due to the finite sampling frequency has been shown to be negligible at the 500-Hz level used in this study (Merri et al. 1990). An erroneous assumption of regularly spaced samples causes distortion, and therefore we used cubic interpolation to recover an evenly sampled RR interval series, from which the PSD estimate was calculated. Short recording epochs (1-2 min) would minimize the likelihood of nonstationarities and permit evaluation of trial-to-trial variance and potential systematic changes over trials (Berntson et al. 1997). The stationarity question was taken into consideration in the current study by minimizing nonstationarities in the data, removing slow trends by filtering procedures, avoiding long analytical epochs, testing for the presence of nonstationarities, and omitting highly nonstationary segments in the data.

A small sample size has its disadvantages. Together with small number of subjects in our study, we failed to detect significant covariate effects of HRV time domain measures in any of the GLM models, which is a somewhat conflicting finding when compared to the literature on normal subjects. However, in the correlation matrix we had significant correlations between age and time domain measures, as expected.

The potential influence of respiration on RSA must also be considered. RSA is a product of both peripheral and central respiratory mechanisms, the latter of which is also related to the origin of high frequency HRV (Berntson et al. 1997). Healthy individuals do not breathe uniformly at a fixed frequency (Priban & Fincham 1965), and experimental conditions may alter respiratory parameters substantially. Even the experimental control of breathing involves mental effort and reduces HRV (Berntson et al. 1997). However, there are also reports in which voluntary control of breathing has no effect on HRV (Hirsch & Bishop 1981). The lack of respiratory measures may not preclude some group contrasts in a well-defined population with known respiratory patterns, when experimental conditions do not alter respiratory parameters appreciably (Berntson et al. 1997). This recommendation is supported by the current data as well, although respiratory coupling itself may be more altered in the behavioural context of our patients than in the controls, and is of interest as such.

6.2.3.3. Auditory event related potentials

A potentially confusing factor when comparing the present results with earlier studies is that the majority of authors have used an oddball paradigm with two types of repeated stimuli and rather small interstimulus intervals, excluding the prominent arousal component observed with our somewhat longer ISIs. We used two different paradigms: a habituation paradigm with trains of four tones and an ITI of 12 seconds, and an oddball paradigm with pitch deviant tones. In both paradigms the ISI was 1 s.

Our oddball paradigm consisted of only the pitch deviance detection task, and thus no evidence of the intensity or duration of deviance processing was obtained. Our preliminary interest was directed at the prospective physiological mechanisms of early psychotic illnesses, which led us to choose a paradigm that not only provided evidence of rough auditory discrimination processes (the pitch deviance was relatively large and the task was easy) and orienting but had also previously produced evidence of intact functioning in schizophrenia (O'Donnell et al. 1994, Kathmann et al. 1995a).

6.2.3.4. Face P300 paradigm

The visual face stimuli were sufficiently attention-capturing to keep the subjects focused on the task throughout the session. We found visual ERP components with earlier latencies than in previous studies (Bentin et al. 1999b, Mouchetant-Rostaing et al. 2000a). The early latency found in this study may be due to the attention task requirements and characteristics of the stimulus. Since 75% of the face stimuli were emotionally arousing (laughing/happy, frightened, angry), they may have maintained the mental alertness of the patient throughout the session and shifted the peak latencies earlier.

We believe that our N145 component largely corresponds to the previously well-known face-related N170 component (Linkenkaer-Hansen et al. 1998, Bentin et al. 1999b, Eimer 2000a, Eimer 2000b, Rossion et al. 2000, Sagiv & Bentin 2001). In controls, our N145 component reached its amplitude maximum in T5 and T6 as in previous studies (Eimer 2000b, Eimer 2000a, Mouchetant-Rostaing et al. 2000a). In contrast, in psychotic patients the maximum was located in the CB1 and CB2 channels, where the between-group difference was also most significant, reflecting a difference in the distribution of the face processing activity in the brain between patients and controls. Our data also revealed the VPP at Cz and channels anterior to it.

Unfortunately, however, we had no non-face stimuli in our recording set, and thus we are unable to indisputably demonstrate that our finding was face-specific.

In our visual oddball paradigm, the smiling faces were targets requiring a motor response. The neutral, angry and frightened faces were standard stimuli. We excluded target responses from the analysis of the face task because of the potential task-dependent attention effects associated with them, since we assumed that the differences in selective attention in the psychotic and healthy state might have masked the possible differences in responses to human faces *per se*. We chose to analyze only the "standard" responses to obtain the best possible signal-to-noise ratio.

6.3. Autonomic nervous system findings in acute psychosis

The classical view on the autonomic nervous system followed Claude Bernard's concept of homeostasis and the role of the sympathovagal system, and it was seen through maintenance of energy balance. Another historical approach emphasized the emergency role of sympathetic control (fight or flight), which lead to arousal theories concerning many clinical states, including psychosis and schizophrenia. Since the 1990s the focus of interest in ANS research has been on sympathovagal balance.

6.3.1. Arousal

In general behavioral terms, the level of arousal corresponds to the activation level of the subject (from drowsiness or stupor to intense mental activation or hypermania). Arousal can also be considered as the level of motivation of the organism and its alertness. It has been described in literature in a number of ways, but in current work it is comprehended as a continuum of behavioral and underlying physiological states (Weinman 1987, Berntson & Cacioppo 2000). The role of reticular formation in regulating arousal level is evident, and this modulation can be affected by the level of sensory input and by the individual's emotional/psychophysiological state (Weinman 1987). Arousal concept is often discussed concerning ANS homeostasis, since *e.g.* SSR is particularly a measure of alertness, which may be associated with changes in skin conductance, heart rate and pupil dilatation following novel stimulation. In current work the concept is, however, considered to affect all levels of sensory/perceptual system.

It is well-known that large variation exists in the SSR waveform configuration (Toyokura 1998). However, earlier studies revealed significant uniformities in different responder categories, thus suggesting that specific alteration patterns in SSRs exist during a psychotic disease process (Gruzelier & Venables 1974, Bernstein et al. 1982). Even though the frequency (25-50%) of non-responders in schizophrenia samples could at least partly be explained by medication effects, the characteristic was also linked to negative symptoms (particularly emotional and social withdrawal). Low SSR reactivity

is associated with hypoarousal, which may be in line with our HRV results suggesting changes in sympathovagal balance rather than excessive sympathicotonus.

Our findings indicate considerably more pronounced SSR variability in unmedicated acute psychosis as compared to normal individual variability. It seems justified to characterize the SSR response pattern in acute psychosis as a loss of time-organization of the stimulus-response sequence, which may explain the disorganized and unpredictable autonomic response pattern. In our data, the patient group with low SSR amplitudes (probably ranked as non-responders in other studies) also exhibited visually detectable temporal disorganization of responses. We suggest that timing alterations are more global and stable SSR characteristics of an acute psychosis than hyporesponsiveness itself.

In earlier studies the non-habituation of SSR and high rates of spontaneous fluctuation have been described in drug-free acutely psychotic patients, suggesting hyperarousal (Gruzelier & Venables 1974, Zahn et al. 1979, Zahn et al. 1981b, Zahn et al. 1981a, Frangou et al. 1997). It has also been suggested that spontaneous fluctuation would arise from constant orienting to internally generated stimulation such as hallucinations (Toone et al. 1981). This does not contrast with our hypothesis of profound alterations in the timing of autonomic responses to arousing stimuli.

In the early phase of psychotic illness, physiological compensatory phenomena are likely to exist, maintaining alterations in the arousal level, attentional operations and emotional control. These functions are created by the activation of the same neuronal circuits that control SSRs.

6.3.2. Sympathovagal imbalance and deficient adaptation of autonomic functions

In addition to the study of SSR, which may be reduced to mainly record sympathic activation, arousal and allocation of attentional resources, we examined HRV to clarify the role of vagal input in the homeostasis, or chaos, in psychosis.

Investigation of the autonomic nervous system has a long tradition in schizophrenia. An abundance of conflicting evidence has been reported for a variety of subject populations, experimental procedures, measurement techniques and drug-effects. However, high tonic levels of sympathetic arousal and diminished habituation of the amplitudes of autonomic responses have generally been confirmed (Zahn et al. 1979, Dawson et al. 1994). Toichi et al. (1999) reported no significant differences in the mean RR in chronic schizophrenic patients, although they found a suppression of parasympathetic function during pronounced psychotic symptoms. Since both the RMSSD and HF power are associated with respiratory effects on the heart rate and modulated by both vagal (parasympathetic) and sympathetic activity, our results are consistent with these findings and show the presence of these disturbances already in the early phase of the illness. However, the reduced mean RR in acutely ill patients described by Toichi et al. (1999) was not supported by our results. Thus, alterations in the parasympathetic-sympathetic balance seem to be related to acute psychotic symptoms, although the decrease in overall HRV probably appears only in chronic patients.

Brekke et al. (1995) observed a correlation between negative symptoms and a reduced resting heart rate, although positive symptoms were not related to alterations in HRV variables. They suggested that heart rate variables might represent trait-related aspects of the negative symptoms. Our results are partly in agreement with this view, but our data does not support Brekke's conclusion that HRV changes (specifically in our data RMSSD, NN50, HF power and lack of adaptation according to task connected strain) in acute psychosis could be specific to any symptom cluster.

Our results also suggest the possibility that psychotic illness may increase, via an HRV decrement, the risk of conductance disturbances and arrhythmias in psychotic patients. A lower heart rate regulation capacity could be further amplified by the effects of any antipsychotic or antidepressive drugs that are known to cause impulse conductance disturbances. This may increase the psychotic patients' risk of cardiovascular events. Although such a risk could not directly be evidenced by our results, these findings may provide one potential pathophysiological hypothesis to be

tested in future risk studies.

It seems that, unlike the reciprocal sympathetic-parasympathetic response to orthostatic changes, responses to stress reveal different patterns of correlation. Berntson et al. (1994) have demonstrated individual, cross-task stable characteristics of autonomic responses to stress using pharmacological blockades. Thus, exaggerated cardiac reactivity may arise from distinct modes of autonomic control and also represent a risk factor for cardiovascular disease.

Cardiac chronotropy is a joint function of sympathetic and vagal outflows to the heart, both of which are affected by psychological stressors and vary independently (Cacioppo et al. 1994). An individual's classification as having high heart rate reactivity could be derived from elevated sympathetic reactivity, vagal withdrawal, or reciprocal activation of the sympathetic and vagal outflows to the heart. Similarly, a low heart rate reactivity classification could stem from low sympathetic (and vagal) reactivity, or alterations in the sympathetic and vagal control systems of cardiac chronotropy (Cacioppo et al. 1994). A general increase in the adrenergic activation of the heart is thought to abbreviate the pre-ejection period and elevate the HR, whereas decreased activation of the heart is thought to decrease RSA and increase the HR (Cacioppo et al. 1994). Stress-induced changes in RSA and in the pre-ejection period can vary independently, and each may predict unique autonomic determinants of HR reactivity (Cacioppo et al. 1994).

Few reports have investigated the effect of schizophrenia on HRV adaptation. Although the stress of speaking in public is known to increase the heart rate in both patients and controls, schizophrenics exhibit no significant cortisol response, thus indicating an impaired ability to adapt to task demands (Jansen et al. 1998). Cognitive manipulations have induced an increase in heart rate in normal controls, and a similar increase has been reported in paranoid subjects as a function of task demands (Rippon 1992), whereas other patients with schizophrenia have been shown to display a reduced cardiac response (Steinhauer et al. 1992). Similar findings have been reported for reactivity to sensory stimulation in early psychosis (James & Barry

1980). In childhood onset schizophrenia, higher rates of spontaneous HRs and smaller anticipatory HR responses during rest have been observed in experiments using innocuous tones, and in reaction time tasks (Zahn et al. 1997).

Zahn et al. (1981a, 1981b) reported reduced adaptation of HRV in drug-free patients using a method rather analogous to ours. Under resting conditions, during exposure to auditory stimuli and in an arithmetic task, they demonstrated a decreased responsivity in patients to all conditions: increased resting HR, lower phasic responsivity, less anticipatory activity and a lower tonic arousal response to a stress procedure similar to that reported earlier for acutely ill schizophrenic patients (Fowles et al. 1970). Both of these findings are in close agreement with the results of the present study. However, without power spectral analyses, the origin of ANS alterations may remain unclear, since time domain methods tend to group together several spectral components, each of which may correspond to different physiological processes (Myers et al. 1986). In our data, the time domain measures and spectral analyses were strongly associated and represented similar findings of instability in psychosis.

In summary, our results are in close agreement with those of earlier studies on HRV and psychotic disorders (Fowles et al. 1970, James & Barry 1980, Zahn et al. 1981b, Zahn et al. 1981a, Steinhauer et al. 1992, Jansen et al. 1998, Takahata & Moghaddam 1998, Toichi et al. 1999) and yield new details of the sympathovagal regulatory state of imbalance in acutely ill drug-naïve first-episode patients. Our findings also confirm and extend the previously demonstrated finding of lower phasic and tonic autonomic nervous system reactivity to meaningful or demanding stimuli (Zahn et al. 1981a, Zahn et al. 1981b).

In addition to sympathetic hyperarousal, there seems to be a failure of sympathetic-parasympathetic balance in monitoring heart rate during acute psychosis, not related to anxiety but merely to withdrawal and other negative types of symptoms. The imbalance is associated with decreased short-term fluctuation of HRV and impaired task-dependent adaptation of the subject, and may at least partly, possibly even

predominantly, be of parasympathetic origin. These alterations imply overall readjustment difficulties in balancing between internal and external stimulation during psychosis. Jackson (1974) demonstrated that in schizophrenia there is a threshold effect on the amplitude of HR deceleration, where HR deceleration tended to decrease, increase and decrease again with increasing stimulus intensity. We speculate that imbalance in sympatho-vagal monitoring may be, at least partly, responsible for this threshold effect.

6.4. Event related potentials data – responses to sensory stimulation

6.4.1. Hyperactive automatic detection processes – a landmark of psychosis

Our results indicate that a psychotic state is associated with widespread cerebral hyperactivity during early processing of an arousing auditory stimulus. The altered arousal was also characterized by simultaneous recordings of SSRs, which revealed similar deficits in the adaptation of autonomic nervous system responses to those shown in earlier studies of psychosis (Roth et al. 1980, Levinson 1991, Dawson et al. 1992). In addition to frontally increased N1 amplitudes in patients in the habituation paradigm, the N1 amplitudes were also increased in oddball tasks. In the face oddball, the early visual responses signifying visual detection processes (P92 component) did not differ between the groups, which is consistent with an earlier report on intact VEPs (visual evoked potentials) in first-episode psychosis (Katsanis et al. 1996). Early visual ERP components as well as the early auditive processing are considered more specific to the physical properties of the stimuli rather than the psychological meaning or cognitive processes related to stimulation.

The reduction of the N1 amplitude in schizophrenia is well-documented (Shelley et al. 1999, Potts et al. 1998), and the N1 amplitude decrease seems to vary between the

diagnostic subgroups of schizophrenia (Kessler & Steinberg 1989). However, the effects of clinical state and medication are as yet unclear; one study has reported no change in the N1 amplitudes after 4 weeks of antipsychotic medication despite significant clinical improvement (Ford et al. 1994), whereas Adler et al. (1993) reported that 2 weeks of haloperidol treatment significantly decreased N1 amplitudes. Only one study of acute state schizophrenia seems to exist showing shortened N1 latencies (Schlor et al. 1985), in agreement with the current finding of shortened latencies associated with evident hyperarousal. However, the differences were not detectable after a period of haloperidol treatment and symptomatic recovery. We conclude that a chronic N1 decrement seems to be an unchangeable state, but in the early state of underlying disorder, the N1 rapidly reacts to changes in the psychophysiological state of a person and to medication.

We consider our somewhat different findings from previous studies, such as increased ERP amplitudes, to be related to the early and acute phase of the disease process and the drug-naïve condition of the patients. There was no difference in the N1 amplitude distribution between schizophrenia *vs.* non-schizophrenia subgroups in any of the three paradigms used (III, IV, V), suggesting that the hyperactivity is a global phenomenon related to early acute psychosis *per se*. This strongly supports the initial hypothesis of altered state of arousal being one potential unifying feature of a psychotic state rather than any specific DSM or ICD (International Classification of Diseases) diagnosis.

6.4.1.1. Orienting throughout the test – impaired novelty processing

Human hippocampal structures are involved in novelty detection (Knight et al. 1989b), *i.e.*, in the ability to optimize the response to unexpected stimuli ("the orienting response"; (Sokolov 1975, Knight 1984)). Novel stimuli also activate a distributed network involving prefrontal and posterior association cortices (Knight 1984, Knight et al. 1989a, Yamaguchi & Knight 1991), which is impaired in schizophrenia (Bachus et al. 1997, Fletcher 1998). In our data, the patients exhibited continuous novelty-like orienting throughout the recording session revealed by both persistent sympathetic skin responses and the enlarged amplitudes of the auditory N1. We speculate that the

hyperactivity of the psychotic patients may arise from the "nonspecific" arousal component overlapping the N1. Since the magnitude of the N1 is shown to be dependent on the validity of the stimuli (Mangun & Hillyard 1991), the behavioural significance of the stimulus may be different for a psychotic patient. The situation in psychosis may also stress the defense reaction system (DR): the stimulation may appear intensified due to gating deficits or a habituation decrement (Jackson 1974, Gruzelier et al. 1981, Adler et al. 1985, Iacono 1987, Adler 1991, Braff et al. 1992, Griffith et al. 1993, Smith et al. 1994, Braff et al. 1995, Griffith et al. 1998, Cadenhead et al. 2000).

6.4.1.2. Hypernegativity – automatic preparation

We found a stable additional negativity starting from 100 ms and remaining through the rest of the epochs in all three ERP paradigms. It was especially prominent in the auditory oddball paradigm for the deviant stimuli. This hypernegativity may, at least partly, explain the persistent MMN (revealed by the maximum amplitude of the subtraction waveform within the time window of 100-200 ms poststimulus, (IV)) in our patients as well as the N1 enhancement (revealed by both maximum and mean amplitudes in the auditory oddball data within the "N1" window and in the habituation paradigm (III, IV)), both of which are somewhat contradictory findings when compared to previous literature (Ogura et al. 1991, Javitt et al. 1993, Ford et al. 1994, Javitt et al. 1995, Todd et al. 2000).

We consider the phenomenon to have close similarities with "processing negativity" (Näätänen 1982). The later negative shift, peaking at about 400 ms, might be associated with a "sensitization process", which might be an automatic preparation for detecting possible subsequent stimulus changes (Alho 1995). In our study, this process appeared to be emphasized in acute psychosis, suggesting an accelerated context updating. Furthermore, late negativity has earlier been confined to a condition in which subjects were distracted by task-irrelevant frequency deviations (Schroger & Wolff 1998), resembling the distractibility in psychosis, where attention is constantly interrupted by irrelevant internal and external impulses, at least partly related to gating

deficits.

6.4.1.3. Mismatch negativity – enduring echoic memory

There are two neural mechanisms triggering involuntary attention towards acoustic novelty and change (Alho 1995): a transient-detector mechanism activated by novel sounds and reflected in N1, and a stimulus-change detector mechanism reflected in MMN (Escera et al. 1998). Generators for both of these responses are mainly located in the auditory cortex with a weak frontal component (Giard et al. 1990, Csepe et al. 1992, Tiitinen et al. 1993, Alho 1995, Näätänen & Alho 1995a, Deouell et al. 1998, Rinne et al. 2000). A sound markedly differing in frequency may elicit an enhanced supratemporal N1 component (Alho 1995). Kreitschmann-Andermahr (1999), however, also found a deficient generation of MMNm in both small and wider pitch changes in schizophrenia. The 1 s ISI we used may point towards alterations in the N1 generator system, and it has been demonstrated that the N1 deficit may increase with increasing ISI associated with a decrease detected in maximal current flow in schizophrenia (Shelley et al. 1999). Our results also indicate this type of reduced brain activity, revealed by a clear deficit in patients' MNE maps.

The MMN alterations in schizophrenia have been demonstrated in several previous studies, and the finding has been extended to unmedicated (previously medicated but drug free at the recording phase) and medicated patients and even to first-degree relatives of schizophrenic patients (Catts et al. 1995, Todd et al. 2000, Michie 2001). In particular, duration deviance detection seems to be severely disturbed in schizophrenia, while the findings concerning large frequency deviants have been more questionable (O'Donnell et al. 1994, Kathmann et al. 1995a). Oades et al. (1997) found an MMN decrement using large frequency deviants, but they argued that in the N1 latency range, as studied by Kathmann and O'Donnel (O'Donnell et al. 1994, Kathmann et al. 1995a), there were no differences between the patients and controls (Oades et al. 1997, Michie 2001). It has been suggested that the degree of deviance and the deviant probability could alter the MMN deficit in schizophrenia (Javitt et al.

1998) and, although not watertight, the hypothesis of large frequency deviants starting up different processing networks (Michie 2001) may provide one example of the multidimensionality of the auditory deviance detection processes. There is recent evidence of impairment in frontal but not temporal components of MMN in medicated patients with schizophrenia (Baldeweg et al. 2002).

The selected method of measuring electrical brain activity within time-windows instead of using traditional components somewhat restricts our opportunity to compare our findings with earlier literature, especially when it comes to MMN. The standard responses of the auditory oddball were alike in patients and controls within "N1" and "MMN" time-windows, but there was a striking difference between the groups during the later processing ("N2b", "P3a" and "P3b"). In deviant responses, the hypernegativity seen in patients was also increasing amplitudes within the "MMN" latency range.

There is a strong relationship between MMN amplitude and/or latency and behavioral discrimination ability (Sams et al. 1985, Singh & Knight 1990, Novak et al. 1992, Lang et al. 1995). MMN implicates accurate neural representations of the preceding stimuli and may serve as an index of these stimulus representations (Näätänen 1995), whereas N1 merely describes afferent mechanisms. Rapid emergence of the memory trace underlies stimulus perception and is formed by integrated feature-specific afferent systems forming the "temporal window of integration". The potential timing disturbances in responses during psychosis previously demonstrated in sympathetic skin responses (I) may also contribute to auditory responses by altering overlapping and the superimposition of cerebral components within the time windows chosen for current analyses.

6.4.2. Altered attention-dependent sensory processing

Our findings can also be discussed in terms of deficient attention capabilities, such as divided attention (psychotic patients fail to divide attention between coping with the

testing situation, and stimuli delivered by microphone) and sustained attention (psychosis is a state with a permanent attention deficit lasting hours to days affecting sensory processing), in addition to short-term attentional processes. The prefrontal cortex includes a central executive system to control attention (D'Esposito et al. 1995), and the inhibitory control of orbitomedial prefrontal cortex protects the active memory from external or internal interference, much as focused attention inhibits distractions from sensory channels (Fuster 1997). Moreover, a disinhibition or loss of inhibitory control can be selective for particular cognitive functions such as attentional selection (Dias et al. 1996) or affective processing (Dias et al. 1997). We believe that an impairment of these inhibitory mechanisms may establish the observed picture of low-amplitude unresponsive stimulus-locked SSR and simultaneous cerebral hyperactivity in acute psychosis.

Attention deficits revealed by slow reaction times, high error rates and P3 decrements have been well documented in schizophrenia (Ford et al. 1992, Andreasen 1999, O'Donnell et al. 1999) and they were also confirmed in the current study (IV). Our findings suggest that there is impairment in the attention-dependent processing of auditory stimuli, also revealed by a poor performance in the discrimination task despite normal psychomotor functioning measured in terms of reaction times in both the auditive and face task. The notion that schizophrenia patients with positive symptoms are positively biased towards the "happy" category, as reflected by their more frequent selection of this category during false recognition (Mandal et al. 1999) needs to be considered. This may have enhanced the attention effects in some of the subjects in our patient group in the face task. To prevent this, we excluded target responses from the final analysis (V) because of the potential task-dependent attention effects associated with them.

The attention deficit may result from a failure in the earlier sensory processing and, for instance, a deficit in sensory memory trace formation, alterations in deviance detection processes, or in attentional processes. In psychotic illnesses, disturbances in focused attention tasks and selective attention are common findings (Shean & Faia 1975, Ikebuchi et al. 1996, Carter et al. 1997, Kasai et al. 1999). Our results are

compatible with all these hypotheses: it is unlikely that the perceptual disturbance in psychotic illnesses could be explained by one single deficit in the sensory system.

The results of behavioral, neurophysiological and cerebral blood flow research confirm that hippocampus and fronto-temporo-limbic circuits are associated with the processing of novelty (Knight & Nakada 1998), partly governed by a pre-attentive sensory memory mechanism (Tiitinen et al. 1994). The anterior cingulate and frontal cortex have an important role in the control of attention (Knight et al. 1989a, Rubin et al. 1991, Berman et al. 1992, Buchsbaum et al. 1992, D'Esposito et al. 1995, Carter et al. 1997, Fuster 1997). Although MMN indicates an attention-independent change detection (Näätänen 1995, Näätänen & Alho 1995c), more complex sound patterns only elicit MMN if they are attended to (Näätänen & Alho 1995b, Näätänen & Alho 1995a) and, once developed, these detection mechanisms become automatic. The N2b-P3a complex is elicited by wider frequency deviants (Schroger et al. 1994), suggesting involuntary attention triggering (Schroger et al. 1994). In our study the large pitch deviance as well as happy faces made the deviants/targets perhaps more attention capturing, thus emphasizing novelty processing. The poor performance despite the easy discrimination task points to an inability of patients to maintain the focus of attention, which may partly explain their persistent orientation compared to the controls. Oades et al. (1997) reported impaired attention-dependent augmentation of MMN in 24 newly-admitted schizophrenic patients and suggested that a reduction in the frontal MMN resulted from the absence of an increase in focused attention. Automatic processing deficits are best seen in situations requiring the activation of controlled attentional processes, whereas our test battery allowed free activation of both automatic and controlled systems in order to reveal their possible compensatory interactions or pathological imbalance in network processes.

In visual tasks, the later activity also reflects stimulus-specific brain processes related to the psychological content of the stimulus, when complex visual stimuli such as faces are perceived (Katsanis et al. 1996, Puce et al. 1999). Interestingly, the amplitude difference between the patients and controls in our data only became evident for components associated with the encoding and recognition processes of face stimuli

(N145 and P230). Increased activity was maintained in the left hemisphere after the N145 during further processing of face stimuli in the patients (P230). The extra activity peak of the mean GFP represents the altered distribution of the activity in our patients for the time window of the face-specific component. It may also represent delayed processing. In a recent imaging study, activation in the fusiform gyri by faces was shown to be strongly affected by the attentional condition (Vuilleumier et al. 2001).

It seems that in acute psychosis there are perceptual distortions in the process related to both face recognition and the passive auditory oddball paradigm, both related and independent of the target-connected attentional activity. Whether these distortions reflect disconnectivity of a general perceptual-attentional-motor matrix recently postulated to be involved in schizophrenia (Andreasen 1999), or indicate disturbance in a more specific set of brain responses remains unresolved. The "timing of firing" may be a crucial factor in perceptual construction.

6.4.2.1. Attention set-shifting – hyperorientation and faulty focusing

In addition to the arousal effects intensifying the processing of stimuli, the processing depends on the amount of attentional capacity available (Coull 1998). Attention deficits are often described in association with psychotic illnesses. However, when it comes to the attentional set shifting related to dopaminergic system, the circle is complete: Impairments in shifting attention typically seen in traditionally medicated patients can also be defined as more effective focused attention, where the reward system plays its mediationg role, too. In our data regarding hyperactivity, this was at least clinically evident: All patients were amazingly focused on the tasks, even if their motivation strategies were in some cases based on psychotic ideation.

Attentional set-shifting may have an important role in creating synchrony via a "binding" effect, as attentional selection controls the information flow that underlies perception. The synchrony of action potentials is suggested to be responsible of the selection of input to the consecutive network levels. The summation effect contributes

to the data transfer to subsequent processing stages, when sensory processes and memory interact to form perceptions (Niebur et al. 2002). Prefrontal functions contribute to bridging temporal discontiguities between elements of the behavioral structure (Fuster 1997). A long interstimulus interval may also imply the kind of attention disorder in which these functions are impaired, although hyperorientation suggests rather an inability to sustain attention even with shorter ISIs.

6.4.2.2. The role of frontal processes

The prefrontal cortex has three functional domains: working memory, executive operations and inhibitory control (Fuster 1997). During the past ten years the pathological alterations concerning both these functions and the underlying anatomical structures (prefrontal cortical areas) have been strongly associated with schizophrenia (Goldman-Rakic 1994, Goldman-Rakic & Selemon 1997, Goldman-Rakic 1999). This was also our motivation for including WCST in our tasks, resulting in a clear performance failure in patients, *i.e.* an increased number of wrong strategies and slower reaction times when compared with healthy controls.

The networks involved in perception and memory share a large number of activated regions, and in addition, the build-up of short-term memory traces most likely occur only at optimal levels of arousal (Cahill & McGaugh 1998). This may relate prefrontal functions to the enhanced arousal level that was observed as enlarged responses, not only during the first "arousing" tone of a train, but also during the first repetitions of the physically identical tones. The dorsolateral prefrontal cortex participates in memory encoding (Fletcher et al. 1998) and in working memory (Rainer et al. 1998). It has been suggested that prefrontal neuronal populations may activate sensory representations in more posterior associative areas via feedback projections (Ungerleider 1995). Indeed, functional imaging studies indicate that the same cortical regions that process sensory information are involved in the active maintenance of memories and in the establishment of associative links between the stored information (Ungerleider 1995), and become activated during hallucinations (Silbersweig & Stern 1996). A conflict in

temporo-hippocampal deviance and/or novelty detection would alter the comparisons of sensory input with the inner representations of perceptual models. This conflict may be based on the asynchrony of input at earlier levels of processing.

The functional significance of memory trace formation is that it provides a continuously updated sensory prediction of the immediate future. These processes are important in psychosis, when a failure in reality-testing forces constant updating of the working memory content. The dorsolateral prefrontal cortex (DPFCx) participates in this memory encoding (Fletcher et al. 1998) and selecting, and in maintaining behaviorally relevant information (Rainer et al. 1998). An enhancement of middle latency auditory-evoked potentials in patients with unilateral DPFCx lesions has been reported (Knight et al. 1989a). This enhancement is associated with reduced DPFCx-mediated thalamic gating of sensory inputs to the auditory cortex. Decreased N2-P3a responses elicited by unexpected novel auditory stimuli have also been demonstrated (Knight 1984, Knight et al. 1989a, Knight et al. 1989b). All these findings are consistent with our results suggesting a potential imbalance in temporospatial deviance detection processes in early psychosis, resulting in behavioral discrimination impairment based on either failure in early sensory memory trace formation or on attention-dependent processes. These can be related to abnormalities in temporo-frontal functions previously well-documented in psychotic illnesses (Weinberger et al. 1986, Catafau et al. 1994, Weinberger et al. 1994, Bogerts 1997, Goldman-Rakic & Selemon 1997, Carter et al. 1998, Fletcher 1998, Andreasen 1999, McDonald et al. 2000, Mathalon et al. 2001).

In addition to the key role of the prefrontal cortex in directing attention to novel events (Daffner et al. 2000), it may be invoved in the generation of the auditory P50, and thus participate in percetual processes on several different levels (Weisser et al. 2001). In animal models the prefrontal cortex is related to selecting and maintaining behaviorally relevant information, which seems to be impaired in our patient sample at least when measured by hyperorienting. More recently, attempts have been made to study the prefrontal functional domains separately in clinical assessments, which has turned out to be methodologically problematic. For instance, the impaired response

inhibition in schizophrenia patients has been associated with both the triggering of inhibitory responses and at the same time with the voluntary initiation of action (Badcock et al. 2002). However, the main link of these functions to our findings probably lies in the central role of the prefrontal cortex in both inhibitory and excitatory regulation of multimodal neural networks (Knight et al. 1999).

6.4.3. Networks in the brain – disintegration in neural circuits in psychosis

Our study provides several implications for disintegration of the responses and alterations in the distribution of cerebral activity. They are revealed by MNE (minimum norm estimate) maps and dipole source analysis models of the activity. The differences shown in the cortical current source density maps between the groups should be considered as such, not as exact virtual locations of the sources of electrical activity, since they were calculated from the group averaged data.

6.4.3.1. Examples from auditive processing

Speculatively, the finding of frontally emphasized cortical activity in psychotic patients most likely reflects hyperactivity in frontal or cingular areas (III). A plausible alternative for this type of activity distribution would be a large deep source such as the thalamus. In both cases the potentially activated neuronal areas are likely to be simultaneously active and interact. However, there are significant differences in the distribution of the electrical brain activity between acutely psychotic patients and normal controls, also suggesting profound differences in the processing networks and, in particular, in the early emergence of cortical arousal.

During discrimination of deviance our patients failed to activate an organized activity pattern the way controls did. The MNE maps of controls demonstrated signs of previously known sources for MMN (bitemporal and frontal activation) (Baldeweg et al. 2002, Jemel et al. 2002). In our paradigm the pitch deviancy was substantial, possibly

revealing deficits in novelty processing, *i.e.* fronto-temporo-limbic networks (Knight & Nakada 1998). On the other hand, it has been suggested that the changing qualities of the discrimination task may start up different MMN processing networks (Michie et al. 2000, Michie 2001). Interestingly, the patients exhibited identical activity pattern to the one of controls at 500 ms poststimulus (360 ms delayed), which indicates further studies on possible delay in auditory processing network activation.

6.4.3.2. Example of visual processing

During face processing the areas with high-amplitude ERPs were also indicated by equivalent dipole source analysis, which agrees well with recently suggested locations of neural responses to facial expressions seen in fMRI (Phillips et al. 1999). The main magnitude difference emerged in the occipitocentral dipole, which was tenfold higher at 145 ms latency (V). The equivalent dipole was located anteriocentrally in the deeper brain structures in the patients, whereas in the controls it was in the superficial occipital cortical area. The location difference may be explained by an increased activity in certain subcortical areas, or by a widespread increased activation of visual networks in psychosis. In either case, the altered activity may reflect a contribution from the subcortico-cortical arousal network, as reported for the auditive system (III, IV). Ponto-geniculo-occipital activity changes may also be involved in our findings. Furthermore, an inappropriate mobilization of attentional resources to face stimuli would probably increase the overall activation level of visual brain areas. Disintegration of visual networks has been previously observed as instability of VEPs (Roemer et al. 1978), which could provide a third possible explanation for our findings and further emphasize the importance of timing in perception formation. These mechanisms are likely to coexist and interact.

The extra activity peak of the mean GFP during face processing also represents the altered distribution of the activity in our patients for the time window of the face-specific component. Haxby et al. (2001) demonstrated that faces have distributed but overlapping representations in the ventral temporal cortex, and Pierce & Courchesne

(2000) have studied autistic patients with fMRI and shown that aberrant face processing also occurs outside the fusiform area, at individually specific neural sites. We regard our finding as yet another example of psychotic patients utilizing deviant and probably suboptimal neural circuitry for seeing faces, possibly affected by disturbance in attentional mechanisms.

The activation level in the neural networks involved in face processing was strikingly high in psychotic patients, and the activation extended over wider brain areas. We speculate that the observed hyperactivity is related to the lack of stable modeling of perceptions in psychosis (Andreasen 1999), and is associated with randomness, not only in thought and behavior, but also in the actual activation scheme of the sensory networks in the brain.

6.4.3.3. Networks – unifying findings

We can agree with the one clear consensus in the schizophrenia literature on a basic unifying concept behind the pathophysiology of psychosis: a fundamental cognitive deficit that arises from abnormalities in neural circuits (Andreasen 1999, Grossberg 2000). Some theories emphasize thalamococrtical reciprocal connections (Andreasen 1999), some emotional centers interacting with perceptual and associative cortices (Grossberg 2000), or temporofrontal interaction (Fletcher 1998). Emotions can even be seen as communicative interaction activating all different levels of the CNS (brain stem, limbic structures and associative cortices), thus being more "holistic" or mammalian than any other cognitive functions (Halgren & Marinkovic 1995).

It is known that among other things electric activity modulates the development of neural circuits and that temporal properties of the electric activation are crucial, but the actual mechanisms remain largely unknown (Stanton & Sejnowski 1989, Huerta & Lisman 1995, Jensen & Lisman 1998). Schizophrenia is a disorder of reduced synaptic connectivity, developmentally or due to degenerative processes, or both (Glantz & Lewis 1997, Saugstad 1998, Harrison 1999, Honer et al. 1999, Kaiser & Gruzelier 1999,

Glantz & Lewis 2000, McGlashan & Hoffman 2000, Sokolov et al. 2000, Tononi & Edelman 2000, Arnold 2001, Hakak et al. 2001, Harrison & Eastwood 2001, Lidow et al. 2001, Bray et al. 2002, Jaskiw & Kenny 2002, Eastwood et al. 2003, Grima et al. 2003, Innocenti et al. 2003). Plasticity can be divided into structural and synaptic (neurodevelopmental *vs.* functional), which can both exist behind the pathophysiology of psychotic illnesses. Synaptic plasticity is particularly associated with activity-dependent processes related to dysfunctional integration or impaired functional specialization (Friston 2002). Electrophysiological studies have demonstrated both short and long-term plasticity in the human auditory cortex (Pantev & Lutkenhöner 2000). The effects of antipsychotic medication have already been related to plasticity changes, both the delayed therapeutic action and neuroplasticity promoting action, which are suggested to modify synaptic connections in psychosis (Konradi & Heckers 2001).

6.4.3.4. Timing and plasticity

The role of the cerebellum seems to be substantial in the timing of anticipation, co-ordination and sequencing of both sensory and motor functions (Courchesne & Allen 1997, Tesche & Karhu 2000b), as well as in the generation of SSR (Critchley et al. 2000). Recently, the involvement of emotional and attentional cues in the generation and representation of peripheral SSRs have been suggested to modulate the activation of these complex networks (Critchley et al. 2000). In psychosis, all these functions may cause symptoms independently. Our data imply that the observed temporal disintegration may be a neurocognitive marker of psychosis related to abnormalities or misconnections in timing circuitry (I, IV).

Recently, timing-based mechanisms for at least system level plasticity have been brought up (Fox 2000) and related to the cortical processing of orientation (Yao & Dan 2001). It has been suggested that the firing rate, spike timing and number of coincident afferents jointly determine synaptic plasticity (Sjöström & Turrigiano 2001). Working memory and attentional states are determined by selective gating of, for example, frontal and hippocampal systems. This temporal binding may be associated with 40-Hz

synchronization of neuronal discharges (synchronous gamma activity) or synchronous oscillations in the lower spectrum. These phenomena are also related to long-distance inter-hemispheric plasticity (Newman & Grace 1999, Lee et al. 2003). The issue of temporal dynamics in neural systems appears highly relevant concerning psychotic illnesses.

6.4.4. Future studies

The inability to select a "stream" of conscious episodes in psychosis and aforementioned themes concerning neural mechanisms of unconscious cognitive processing, plasticity, mirroring, and integrative psychophysiology are the world-wide challenges of today and tomorrow.

Here in Kuopio the work will continue in searching for more event-related markers of different processes, dealing with the component structure of the potentials, and in an effort to test and develop biosignal analyses. Based on current findings, the results concerning novelty processing (the effects of orienting in novelty responses), and the responses from the WCST (behavioral, SSR/HRV and EEG) are particularly interesting and will probably add complementary new findings to these results. The effects of disease process and the treatments would need a follow-up study, and the clarification of the specificity issues calls for further studies with diverse samples of other psychiatric disorders but psychosis (*e.g.* to reveal a potential stress-hormone related general effects in common with schizophrenia and post-traumatic disorder). Future studies should also aim at clarifying the sex-related differences of current findings as well as the potential differences between the diagnostic subgroups.

6.5. Concluding remarks

I A combination of electrophysiological tests involving recordings of both autonomic nervous system and electroencephalogram, and using a varied range of samples of active and passive paradigms, provides a thorough picture of acute psychosis as a psychophysiological state, when the study group consists of drug-naïve acutely ill first-episode patients enabled by the noninvasiveness and practical adaptability of the method.

II Drug-naïve first-episode patients with acute psychosis suffer from a decreased short-term variation in the heart rate and impairment of heart rate adaptation to an increase in mental load, indicating a disturbance in the sympathovagal balance in their autonomic nervous system that is also verified by their loss of time-organised sympathetic skin reactions.

III First-episode psychotic patients do not exhibit decreased amplitudes of primary sensory responses: both early auditory and visual processing were characterized by hypernegativity and increased amplitudes.

IV The attention-dependent components of auditory event-related potentials are attenuated in psychosis, but face processing is increased in activity, indicating both markers of hyperarousal and alteration in attentional balance.

V There are clear differences between psychotic patients and healthy controls in the distribution of brain activity revealed in early auditory processing, during deviance discrimination processes and visual processing of faces.

7. General conclusions

Psychosis is an expansive and serious clinical state with direct and indirect influences on the entire health of a person. It can hardly be regarded just as a state of mind. To better comprehend the multiple dimensions of the concept of psychosis, there is room for new aspects and terminology in psychiatric research. Interdisciplinary approaches may provide an opportunity for new horizons, which will hopefully lead to more comprehensive conclusions about pathophysiology, or at least enrich the field by more interaction between scientists with divergent expertise. At its best, advanced psychophysiological research could also provide tools for creating new methods for the special cognitive rehabilitation of psychiatric patients in the future.

The main findings of our study share three common denominators, which we suggest are psychophysiological key characteristics of an acute psychotic state: 1) disturbance in the timing of electric input that produces an indistinct and obscure preform for further processing, 2) asynchrony in forming and reforming event-dependent networks resulting in unoptimal wiring, and 3) inappropriate alterations in plastic changes for cognitive functions that complete the cascade. This triangle provides an outline for information processing in acute psychosis.

By now we can see the existing knowledge as a reminder of the importance of thorough clinical investigation of each patient. The patient needs to be treated as a whole individual, not as a summation of his parts. Instead of sticking to rigid nosological systems, careful observation and description of psychopathology should be favored. In an acutely psychotic person, consciousness and reality are the complex of functional problems that the psychiatrist can try to comprehend as a lack of seamless global subjective awareness.

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