Department of Psychiatry, University of Helsinki
Helsinki, Finland

Motor activity measured by actometry in neuropsychiatric disorders

Katinka Tuisku

Academic dissertation

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Supervised by

Senior Lecturer Hannu Lauerma, MD, PhD, Department of Psychiatry, University of Turku

and

Professor Kristian Wahlbeck, MD, PhD, Department of Psychiatry, University of Helsinki

Reviewed by

Senior Lecturer Christer Hublin, MD, PhD

and

Senior Lecturer Timo Partonen, MD, PhD

Opposed by

Professor Erkka Syvälahti, MD, PhD

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Look at the cloud-cat, lapping there on high
With lightning tongue the moon-milk from the sky!

Yogesvara

To my Mai

LIST OF ORIGINAL COMMUNICATIONS

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I. Tuisku K, Lauerma H, Holi M, Markkula J, Rimon R. Measuring neuroleptic-induced akathisia by three-channel actometry. Schizophrenia Res 1999; 40:105-110.

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CONTENTS

ABBREVIATIONS

ACh	acetylcholine
ADHD	attention deficit hyperactivity disorder
ASP	antisocial personality disorder
BARS	Barnes Akathisia Rating Scale
CRA	controlled rest-activity
D	dopamine
DIA	drug-induced akathisia
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
EMG	electromyography
EP	extrapyramidal
GABA	gamma-aminobutyric acid
5-HT	5-hydroxytryptamine
HVA	homovanillic acid
HUCH	Helsinki University Central Hospital
IRLSSG	International Restless Legs Syndrome Study Group
NA	noradrenaline
NIA	neuroleptic-induced akathisia
NSS	neurological soft signs
OCD	obsessive compulsive disorder
PAM	piezoelectric activity monitor
PD	Parkinson's disease
PET	positron emission tomography
PLM	periodic limb movements
PLMD	periodic limb movement disorder
PLMS	periodic limb movements in sleep
RLS	restless legs syndrome
SCID	structured clinical interview for diagnosis
SCSB	static charge sensitive bed
SD	standard deviation
TA	tardive akathisia
TD	tardive dyskinesia
WURS	Wender Utah Rating Scale

1. SUMMARY

In the overlapping areas of psychiatry and neurology, there are several disorders with motor symptoms that can be measured objectively to assess symptom severity or to understand pathophysiological mechanisms. Motor restlessness is an important but often poorly recognized and misdiagnosed symptom.

Neuroleptic-induced akathisia (NIA) and restless legs syndrome (RLS) are hyperactive movement disorders, whereas attention deficit hyperactivity disorder (ADHD) and Asperger's disorder are developmental disorders with prominent motor symptoms. Measuring motor activity by actometry (detects acceleration) is hypothesized to give abnormal findings in all of these disorders. In addition, an objective marker and a measure of symptom severity are needed for NIA and RLS.

The main outcome parameter in this study was lower-limb activity during 30 min of rest in a standardized setting (controlled rest-activity). Fifteen schizophrenic patients with NIA, 15 antisocial personality disorder (ASP) patients with ADHD, 15 RLS and 10 Asperger's disorder patients, and 35 healthy controls were included.

The increase of controlled rest-activity was manyfold (10-85x) and significant in all patient groups compared with healthy controls. It discriminated with no overlap the NIA and ASP/ADHD groups but not the RLS and Asperger groups from healthy controls. A significant decrease of activity to the level of healthy controls occurred in NIA patients during remission. All patient groups, except the RLS group, showed the rhythmic, episodic activity pattern previously reported in NIA. This was most readily seen in the NIA group. A pathognomonic periodic limb movement pattern at 5- to 90-s intervals was found in RLS.

The results demonstrate that rest-activity is abnormal in NIA, RLS, ASP/ADHD and Asperger's disorder patients. Rest-activity measured by actometry can be used as a diagnostic marker and a measure of symptom severity in the two movement disorders (NIA and RLS), and it may be useful in symptom assessment and understanding of the pathophysiology of Asperger's disorder and ADHD. Actometry enhances the objectivity of neuropsychiatric assessment.

2. INTRODUCTION

2.1. Human motor activity

Gravity and continuous motion appear to exist at enormous dimensions, like in clusters of galaxies, as well as at the microlevel of atoms, and everywhere in between. Human life, surrounded by an ever-moving universe, consists of movements both at the microlevel of ions, molecules, genes and cells and at the macrolevel of vital functions, self-regulation, adaptation to environment and communication. The macrolevel movements are mediated by the activity of vegetatively innervated inner musculature or by cortically innervated skeletal muscles. Motor activity, a crucial sign and prerequisite of neural development, is observed very early in the life of the human foetus, right after the limbs have appeared by the 7^{th} gestational week (Connolly and Forssberg 1997).

A major product of the elaborate information processing in our brain is the modulation of contractile force in our skeletal muscles. The motor systems transform neural information into physical energy by issuing commands that are transmitted by brain stem and spinal cord to skeletal muscles. This is the reverse of the sensory systems, which transform physical energy into neural information. They supply a continuous flow of sensory information to the three hierarchical levels of motor control: the motor cortex, brain stem and spinal cord. These hierarchical mechanisms of motor control are integrated by several parallel mechanisms (Ghez 1991a).

Human movements can be divided into three overlapping classes: voluntary movements, reflex responses and rhythmic motor patterns. Purposeful, voluntary movements are under cortical control, but their performance is also regulated by the lower levels, including the brain stem and spinal cord. The lower levels of the motor control system are capable of generating reflexes and rhythmic motor patterns. The reflexes are involuntary responses to a specific stimulus. The automatically sustained rhythmic motor patterns may be initiated and terminated voluntarily (Ghez 1991b).

In addition to the hierarchical organization of the motor cortex, brain stem and spinal cord, other anatomical structures involved in the control of skeletal muscles comprise

the cerebellum, thalamus and basal ganglia. The basal ganglia consist of five interconnected nuclei: caudate nucleus, putamen, globus pallidus, subthalamic nucleus and substantia nigra. The basal ganglia and cerebellum control movements through the mediating actions of the brain stem and thalamic nuclei (Kelly and Dodd 1991). The cerebellum directly regulates execution of movement, whereas the basal ganglia are involved in cognitive aspects of motor control (Cote and Crutcher 1991).

2.2. Extrapyramidal system and its relevance for psychiatry

The basal ganglia are often referred to as the extrapyramidal (EP) motor system, in contrast to the pyramidal motor system of corticospinal tracts. This nomenclature has been criticized because the pyramidal and EP systems are not independent but are extensively interconnected, and other parts of the brain are also involved in voluntary movements. The term EP system is still used, however, and the clinical motor manifestations of basal ganglia dysfunction are referred to as “extrapyramidal symptoms”. These can be classified as positive symptoms or signs, including involuntary movements and rigidity, and as negative symptoms, including bradykinesia and loss of postural reflexes resulting in imbalance (Lindsay et al. 1986). The role of basal ganglia in controlling movements includes several aspects, such as selective facilitation or suppression of movements, initiation of internally generated movements, execution of stereotyped movements and planning of complex motor strategies (Cote and Crutcher 1991, Canales et al. 2000).

Recent anatomical studies have challenged the view that basal ganglia are solely concerned with motor control; they also seem to be involved in different aspects of behaviour and regulation of emotion (Middleton and Strick 2000). This is understandable since the basal ganglia have extensive connections with the association cortex and limbic structures (Cote and Crutcher 1991). The caudate nucleus and the putamen of basal ganglia together form the dorsal part of the striatum, also called the neostriatum, whereas limbic areas make up the ventral part of the striatum. The major components of the EP system comprise neostriatum, globus pallidus, substantia nigra, and the subthalamic nucleus (Borison and Diamond 1987). The connections between the amygdala and ventral striatum mediate limbic emotional and instinctive neural impulses to the motor systems of the basal ganglia (Graybiel

2001). The limbic autonomic and endocrine homeostatic regulation of the hypothalamus is mediated to the basal ganglia through the thalamus (Kupfermann 1991).

The great diversity of neurotransmitters in the basal ganglia, especially in the striatum, is probably needed for complex modulation of behaviours on the basis of sensorimotor, memory-related or conditional cues derived from the neocortex and limbic systems (Graybiel 2001). The transmitters found in the basal ganglia include at least dopamine (D), acetylcholine (ACh), 5-hydroxytryptamine (5-HT), noradrenaline (NA), gamma-aminobutyric acid (GABA), adenosine, homovanillic acid (HVA), glutamate, neurotensin, substance P, enkephalin, dynorphin and cholecystokinin (Lindsay et al. 1986, Borison and Diamond 1987, Cote and Crutcher 1991, Ferre 1997, Huang and Hanson 1997, Reiner et al. 1999). Dopaminergic function in the dorsal striatum is involved in different aspects of motor behaviour than in the ventral striatum. Basal dopaminergic activity in dorsal striatum appears necessary for normal EP functions, such as execution of learned motor programmes, whereas stimulation of limbic dopaminergic transmission in the ventral striatum is essential for motivational motor behaviour (Di Chiara et al. 1992).

Theories of neurotransmitter functions and interactions in basal ganglia are mostly based on animal studies. The interbalanced, reciprocal system of D and ACh is the best understood. An excess of D or depletion of ACh will result in chorea-type movement disorders, whereas an excess of ACh or depletion of D produces parkinsonism (Lindsay et al. 1986). In clinical pharmacology, the reciprocal system allows the antidopaminergic action in basal ganglia to be antagonized by anticholinergic actions (Pearl et al. 1976). EP movement disorders, however, involve more than simply a reciprocal balance between D and ACh (Borison and Diamond 1987). 5-HT activation has an antagonistic effect on the dopaminergic EP function (Carter and Pycock 1979), while the excitatory glutamate system increases striatal dopaminergic function and thereby induces EP motor activation (Sacaan et al. 1992). An antagonistic interaction between D and adenosine seems to exist in the striatum (Ferre 1997).

The extrapyramidal (EP) system, responsible for integration of homeostatic, motivational and cognitive aspects of movement regulation, is of interest in psychiatry for several clinical reasons:

1. Abnormal findings of basal ganglia pathology in several psychiatric disorders such as schizophrenia (Menon et al. 2001), autism (Jacobson et al. 1988, Sears et al. 1999), retarded depression (Martinot et al. 2001), obsessive compulsive disorder (OCD) (Rauch et al. 2001) and attention deficit hyperactivity disorder (ADHD) (Semrud-Clikeman et al. 2000), and in alcoholic violent offenders (Kuikka et al. 1998).

2. EP motor effects of psychoactive drugs, like the neuroleptic-induced movement disorders including parkinsonian symptoms, akathisia, tardive dyskinesia, and dystonias (Cunningham Owens 1999) and the psychostimulant-induced motor activation mediated by enhanced dopaminergic activity in the striatum (Graybiel et al. 1990, Ferre 1997).

3. Psychiatric symptoms are commonly reported in diseases of the basal ganglia (Rosenblatt and Leroi 2000). Examples include anxiety, depression, flattened affect, psychomotor retardation and sleep disturbances which are described in Parkinson's disease (Rosenblatt and Leroi 2000, Shulman et al. 2001); dysphoria, irritation, agitation, apathy and anxiety in Huntington's disease (Paulsen et al. 2001); obsessive compulsive symptoms, other anxiety symptoms, depression, attention deficits and disruptive behaviour in Tourette's disorder (Coffey and Park 1997), psychomotor retardation, amotivation, affective flattening and restlessness in striatal infarcts (Habib and Poncet 1988, Kumral et al. 1999); apathy, disinhibition, dysphoria and anxiety in progressive supranuclear palsy (Litvan et al. 1996) and incongruous behaviour, irritability and aggression in Wilson's disease (Dening and Berrios 1989). Traumatic striatal injury may cause symptoms of OCD and ADHD (Hendler et al. 1999, Herskovits et al. 1999).

The split between neurology and psychiatry about 100 years ago may have contributed to the lack of interest in motor abnormalities in psychiatric disorders until the EP adverse effects of the newly discovered antipsychotic drugs of the 1950s drew attention to motor symptoms in psychotic patients (Beier 1997). Due to the typical

receptor action profile of conventional antipsychotic drugs, the EP adverse effects were first considered to be an essential sign of sufficient dosage for treatment response (Haase 1978). The drug-induced motor disturbances were so common that the possibility of primary EP dysfunction in psychotic disorders was dismissed for several decades (Beier 1997). Recent studies report that 17-21% of neuroleptic-naive schizophrenics show parkinsonian symptoms in clinical evaluation (Caligiuri et al. 1993, Chatterjee et al. 1995). The affective flattening, psychomotor retardation and impairment of cognitive executive functions described in primary Parkinson's disease (Marsh 2000, Rosenblatt and Leroi 2000) are also encompassed within schizophrenia symptomatology (American Psychiatric Association 2000, Jogems-Kosterman et al. 2001).

2.3. Abnormal motor function in neuropsychiatric disorders

Neuropsychiatry is a discipline that seeks to understand the relationships between psychiatric symptoms, neurological symptoms and brain pathophysiology (Lyketsos 2000). As the field of neuropsychiatric research and understanding grow (Lyketsos 2000), the traditional distinction between "organic" and "functional" psychosyndromes is being questioned (Beier 1997). An increasing amount of neuropathology has been found behind the psychiatric disorders classified in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association 2000). The psychiatric classification system also includes primarily neurological diseases, such as different types of dementia, of an identified organic aetiology with predominant neurological and neurocognitive symptoms. At the other end of the continuum are disorders considered to be primarily psychogenic or functional (Beier 1997), and between the two extremes is a large number of neuropsychiatric disorders with neurological signs and some evidence of organic neuropathology, but in which the pathophysiological mechanisms remain unclear. The motor disturbances in psychiatric disorders are obvious clinical signs of brain organic pathophysiology (Beier 1997). Studies on abnormal motor function are useful in constructing pathophysiological hypotheses and may benefit the clinical assessment of neuropsychiatric disorders.

2.3.1 Neurological soft signs, extrapyramidal symptoms and stereotypies

Motor abnormalities are studied, for example, in schizophrenia, autistic disorders and ADHD, all of which are considered neurodevelopmental disorders (Weinberger 1995, Taylor 1999, American Psychiatric Association 2000, Tanguay 2000). Minor motor abnormalities, called "soft signs", are commonly encountered in each of these disorders (Jones and Prior 1985, Aronowitz et al. 1994, Flashman et al. 1996). While the clinical significance of neurological soft signs (NSS) is ambiguous, they are widely regarded as an indicator of non-specific brain damage, although subcortical structures like basal ganglia have been speculated to be associated with them (Kennard 1960). The NSS include abnormalities in gait, balance, laterality, motor co-ordination and integrative sensorimotor functions (Krebs et al. 2000). The term "soft sign" has been criticized for having ambiguous boundaries (Sanders and Keshavan 1998). By definition, soft signs are neurological abnormalities that are not readily localizable to a specific brain region, while "hard signs", or "major neurological signs", such as reflex asymmetry, provide some indication of the underlying brain systems or regions affected (Sanders and Keshavan 1998).

Though the discriminative value of motor co-ordination, motor intergration and sensory integration factors of NSS is good, there is overlap between the NSS factor of involuntary movements and EP symptoms. Thus, this factor needs careful interpretation when neuroleptic-treated patients are examined (Krebs et al. 2000). Single items from EP symptom rating scales, such as glabellar reflex, tremor and rigidity, are also included in validated NSS examinations (Buchanan and Heinrichs 1989, Krebs et al. 2000). Some researchers report tremor, rigidity and bradykinesia in neuroleptic-naive schizophrenics as idiopathic EP symptoms and signs rather than as NSS (Caligiuri et al. 1993, Chatterjee et al. 1995) and others exclude them from the analysis of NSS (Flashman et al. 1996, Smith et al. 1999).

Stereotypies are involuntary, co-ordinated, patterned, repetitive, rhythmic and purposeless movements, which are encountered in tardive dyskinesia, akathisia, schizophrenia, autism, ADHD, OCD and Tourette's disorder (Tan et al. 1997). The dopaminergic system in basal ganglia is assumed to be involved in production of stereotypies (Tan et al. 1997). The distinction between complex tics and stereotypies

is difficult and sometimes may even be artificial (Stern and Robertson 1997, Tan et al. 1997), although some differentiating features have been described: stereotypies are characterized by less distress and weaker association with psychosocial influence than tics (Stern and Robertson 1997).

2.3.2. Schizophrenia

Both soft signs and hard signs of nearly all functional domains are increased in schizophrenia, the subdomains of motor co-ordination and involuntary movements being the most prominent (Ismail et al. 1998). Because NSS are an intrinsic part of schizophrenia (Browne et al. 2000), a standardized neurological assessment method has been validated for them (Krebs et al. 2000). The NSS are associated with treatment resistance and negative symptoms in schizophrenia (Smith et al. 1999) defined as affective flattening, alogia, avolition, anhedonia and reduced attention (Andreasen 1989). NSS are also correlated with poor neuropsychological performance on motor tasks in test batteries, but do not correlate with general intellectual ability in neuropsychological assessment (Flashman et al. 1996). NSS are also present in never-medicated schizophrenics, but its prevalence is reported to be higher in neuroleptic-treated than in never-medicated patients (Gupta et al. 1995). Both soft signs and hard signs seem to be part of the disease process rather than a medication effect (Gupta et al. 1995, Ismail et al. 1998), although the neuroleptic medication may increase the prevalence of NSS. The interpretation of the medication effects on NSS in these studies (Gupta et al. 1995, Ismail et al. 1998) can be confounded by the overlap between assessed EP symptoms and NSS.

The idiopathic EP symptoms, similarly to NSS (Gupta et al. 1995, Smith et al. 1999), are related to negative symptoms, poor treatment response and susceptibility to drug-induced EP adverse effects in schizophrenia (Chatterjee et al. 1995). Rigidity and bradykinesia have been observed in neuroleptic-naïve patients in clinical evaluation (Caligiuri et al. 1993, Chatterjee et al. 1995), but instrumental examination has also demonstrated subclinical tremor in them (Caligiuri et al. 1993). Spontaneous dyskinesia, phenomenologically identical to neuroleptic-induced tardive dyskinesia, is also reported to exist in neuroleptic-naïve schizophrenics (Fenton et al. 1997, Fenton 2000). The prevalence of spontaneous dyskinesia seems to be associated with the age

of patients (Fenton 2000), being significantly higher in schizophrenia patients as compared with other neuroleptic-naïve psychiatric patients. The non-schizophrenic patients most often affected are those diagnosed with a schizophrenia-spectrum disorder, or bipolar disorder (Fenton et al. 1997). The presentation of idiopathic EP symptoms in schizophrenia may be related to low baseline dopaminergic activity in subcortical areas, including the basal ganglia, which has been suggested to be a pathophysiological prerequisite for dopaminergic sensitization leading to full symptomatology (Glenthöj and Hemmingsen 1997). Thus, the conventional neuroleptics treat the positive psychotic symptoms at the cost of further basal dopaminergic hypofunction (Glenthöj and Hemmingsen 1999).

Catatonic motor behaviours are classified as characteristic positive symptoms of schizophrenia including catatonic stupor, -rigidity, -negativism, -posturing and -excitement (American Psychiatric Association 2000). Motor poverty, dyskinetic symptoms and stereotypies are more strongly associated with schizophrenia than with other psychotic disorders (Peralta and Cuesta 2001). The prevalence of motor symptoms seems to decrease in hospitalized patients while the psychotic episode is treated (Peralta and Cuesta 2001). The reduced psychomotor activity related to negative symptoms of schizophrenia is connected with EP symptoms in assessment by rating scales due to an overlap of symptom descriptions. Objective EP signs are more difficult to differentiate from negative symptoms by assessment scales than subjective EP symptoms (Dollfus et al. 2000).

2.3.3. Neuroleptic-induced movement disorders

The neuroleptic-induced EP symptoms include parkinsonian symptoms, akathisia, tardive dyskinesia (TD), and acute or tardive dystonia (Cunningham Owens 1999), which are defined in DSM-IV (American Psychiatric Association 2000). This classification also includes neuroleptic malignant syndrome in the category of medication-induced movement disorders, although autonomic symptoms, disturbances of consciousness, and possible impairment of vital functions are clinically more relevant than the concomitant muscle rigidity, which may resemble catatonia. Addition of the category medication-induced movement disorders not otherwise specified in DSM-IV, acknowledges that drugs other than neuroleptics can

also cause comparable EP movement disorders (American Psychiatric Association 1994, Leo 1996).

Akathisia is a state of motor restlessness with subjective feelings of inner restlessness (Sachdev 1995a); for further description, see section 3.1. TD is characterized by abnormal, involuntary movements, which are typically choreiform, choreoathetoid or rhythmic and stereotyped (American Psychiatric Association 2000). The reported increase of TD with age and years of neuroleptic exposure may be in part accountable for the age-related increase of spontaneous dyskinesia misinterpreted as neuroleptic-induced dyskinesia (Khot and Wyatt 1991). Neuroleptic-induced dystonic movements include abnormal positioning or spasms of the muscles in the affected body part (American Psychiatric Association 2000).

The iatrogenic, neuroleptic-induced parkinsonian symptoms are bradykinesia or hypokinesia, rigidity and tremor. The motor symptoms in neuroleptic-induced parkinsonism, known also as secondary parkinsonism, are slightly different from those in primary Parkinson's disease (PD) (Cunningham Owens 1999): bradykinesia is a dominating symptom in secondary parkinsonism, whereas in PD it is essential mainly in the upper body. Rigidity is more severe and progressive in PD than in secondary parkinsonism, in which it is often mild or moderate, typically requiring reinforcement to be detected. Resting tremor is present in the majority of PD patients, while it is a rare, late manifestation of secondary parkinsonism. Postural tremor, by contrast, is a common, early manifestation of secondary parkinsonism. Furthermore, the motor symptoms seem to be more lateralized in PD than in secondary parkinsonism.

2.3.4. Restless legs syndrome (RLS)

The category of dyssomnias in the psychiatric classification of DSM-IV also includes idiopathic RLS (for clinical description, see section 3.2.), a movement and sleep disorder (Amar 2001), which has often been misdiagnosed as a psychiatric disorder because of its secondary effects on sleep and mood (Chokroverty and Jankovic 1999). Today, it is considered to be an independent neurological disorder (Winkelmann 1999). The most studied motor abnormalities related to RLS are periodic limb

movements in sleep (PLMS), which are common but non-essential features of RLS (IRLSSG 1995). Motor restlessness, one of the key features of RLS (IRLSSG 1995, Table 2), includes both a component of involuntary periodic limb movements (PLM) and a component of voluntary movements in response to sensory symptoms (Montplaisir et al. 1998). The motor restlessness and subjective discomfort related to RLS are modulated by circadian rhythm, being maximal in the night-time and minimal in the daytime (Hening et al. 1999b). Both RLS and nocturnal akathisia are claimed to be common sleep disturbances in Parkinson's disease (Stocchi et al. 2000), but there seems to be some overlap in their descriptions (Sachdev 1995a). Moreover, a recent clinical study shows that the motor restlessness in Parkinson's disease patients seems to be related to akathisia rather than RLS when standard diagnostic criteria are applied (Tan et al. 2002).

2.3.5. Attention deficit hyperactivity disorder

NSS in low-birthweight children seem to predispose them to attention deficits (Breslau et al. 2000). They can be helpful in differentiating the children at risk for developing ADHD (Vallee and Pandit 1991). An increased presentation of NSS appears to be related to ADHD with or without a comorbid conduct disorder but not to conduct disorder alone (Aronowitz et al. 1994). Hyperactivity is correlated with inattention in ADHD (Dane et al. 2000), but it is considered to be a primary feature of ADHD, instead of merely being a secondary effect of inattention (Porrino et al. 1983a). The impairment of motor skills does not explain the hyperactivity detected (Porrino et al. 1983a). Motor hyperactivity is present in ADHD independent of subtype and seems to be related to situations demanding self-regulation (Dane et al. 2000). It is the most discriminative feature of ADHD in comparison with other psychiatric disorders (Halperin et al. 1992). Psychostimulants reduce motor hyperactivity (Porrino et al. 1983b), but during medication ADHD children are vulnerable to developing tics (Varley et al. 2001).

2.3.6. Autistic spectrum disorders

Motor disturbances, including NSS, movement disorders and stereotypies, are characteristic of autism (Vilensky et al. 1981, Jones and Prior 1985, Gillberg 1995,

Brasic 1999). Movement disturbances may be essential for the core features of autism because they can have a profound effect on a person's ability to regulate movement to effectively communicate, relate and participate with others (Leary and Hill 1996). The motor impairment in autistic children is more severe than that of children with learning disabilities (Hughes 1996). Asperger's disorder patients appear to have more sensory-motor dysfunction, especially in maintaining their balance, than patients with high-functioning autism at the same cognitive level (Iwanaga et al. 2000). Even Asperger's disorder patients with exceptionally high verbal intelligence may have considerable motor impairment in the form of numerous soft signs and motor tics (Nass and Gutman 1997). The increased caudate volume in high-functioning autism seems to be positively associated with motor mannerisms (Sears et al. 1999).

Basal ganglia have been suggested to be responsible for the force-control component of clumsiness, reported in Asperger's disorder (Smith 2000) and for parkinsonian-type disturbances of gait, detected in autism (Vilensky et al. 1981). Both autistic and parkinsonian patients display bradykinetic and rigid gait detected as shortened stride lengths, elongated stance phases and reduced joint flexions (Vilensky et al. 1981).

2.3.7. Other disorders

Tourette's disorder, which shows some comorbidity with OCD-, ADHD- and autistic features (Baron-Cohen et al. 1999, Kadesjö and Gillberg 2000), is characterized by involuntary motor and vocal tics (American Psychiatric Association 2000). Tics and Tourette's disorder are part of the same spectrum of disorders (Gillberg 1998a). NSS are common in Tourette's disorder (Semerci 2000). Repetitive, stereotyped behaviours typical of both Tourette's disorder and OCD may be related to striato-thalamic dysfunction in these disorders (Rauch et al. 2001).

In OCD, the presentation of high NSS scores is associated with volumetric reduction of brain tissue (Stein et al. 1993a). The severity of OCD symptoms and neuropsychological impairment are correlated with NSS (Bolton et al. 2000). An increased amount of NSS may also be found in some other psychiatric disorders (Stein et al. 1993b, Gurvits et al. 2000), probably indicating a general neuropsychiatric vulnerability related to non-specific brain damage (Kennard 1960).

2.3.8. Pathophysiological considerations

Some evidence exists for dopaminergic and basal ganglia pathophysiology in several neuropsychiatric disorders with abnormal motor function, including schizophrenia (Glenthöj and Hemmingsen 1997, Menon et al. 2001), autism (Jacobson et al. 1988, Ernst et al. 1997, Sears et al. 1999), ADHD (Krause et al. 2000), RLS (Turjanski et al. 1999, Ruottinen et al. 2000), OCD (Lucey et al. 1997, Billet et al. 1998) and Tourette's disorder (Malison et al. 1995, Ernst et al. 1999), but obviously other mechanisms are also involved. The presentation of NSS has not been connected to any specific brain region (Sanders and Keshavan 1998). The evidence for dysfunctional frontostriatal circuits in developmental neuropsychiatric disorders is increasing (Gillberg 1998a). Even EP movement disorders may have origins other than basal ganglia, such as the limbic and motor cortices, which seem to be involved in the pathophysiology of NIA (Ohashi et al. 1998), and the circuits connecting the cortex, thalamus, basal ganglia and cerebellum, which are suggested to be involved in the pathogenesis of involuntary movements and hyperkinesias (Rice and Thompson 2001).

2.4. Measuring motor activity in neuropsychiatric disorders

2.4.1. Methods

Human motor activity can be measured directly as gross and fine three-dimensional movements by accelerometric methods and as electric activity of motor units by electromyography (EMG) and its applications. Actometry and actigraphy are used in the literature as synonyms for recording methods based on accelerometric sensors. Accelerometric applications include both old mechanical and more modern piezoelectric, computerized detectors, and they all react to acceleration signals produced by body movements. The modulation, integration and recording of the signal are varied, as is the output of the data in different types of accelerometric methods and their commercial applications. The ambulatory monitors in accelerometric methods are typically attached to the limbs of the patient in a wrist-watch manner. EMG electrodes measure electrical signals emitted during muscle

contractions. Surface electrodes can detect activity from large superficial muscles, but the more invasive needle or wire electrodes are needed to discriminate activity from smaller deep muscles. The disturbing effect of EMG electrodes on normal moving of the subject has been studied in neurological child patients (Young et al. 1989), and expectedly, the surface electrodes caused less disturbance.

Angular joint movements can be measured by electro-goniometers, which record the relative orientation of two bases connected by an elastic beam (Legnani et al. 2000). The different versions of electro-goniometers include strain gauges (Legnani et al. 2000). Strain gauges are also a component of a force transducer, which measures muscle rigidity (Caligiuri 1994) defined as the ratio of changing muscle force to changing muscle length. A force transducer is attached to the limb of the patient and the external force applied by the examiner to displace the patient's limb is transduced along with rotation (Caligiuri 1994). Other indirect methods of measuring motor activity are, for example, ultrasonographic movement counters (May et al. 1983, Hoff et al. 1999), digital video camera movement analysis (Nilsson et al. 1996), photodetectors (May et al. 1983, Hoff et al. 1999), posturography (Bloem et al. 1998, Lanska 2001), pedometers (Dale et al. 2002) and static charge sensitive beds (SCSB), which record the changes of electric potentials in the mattress of the bed induced by body movements (Alihanka and Vaahtoranta 1979, Kronholm et al. 1993).

In addition to measuring body movements and motor activity of the muscles, other dimensions of motor functions, such as central magnetic or electric potentials, corticospinal excitability and peripheral conduction velocity (Rossini and Mauguire 1990) are measured in neuropsychiatry. Methods of assessing human motor activity also include systematic, direct observations and self-report questionnaires (Dale et al. 2002). Measuring movements and motor activity is common in clinical neurophysiology, neurology and sleep medicine, but it has also been utilized in psychiatry, geriatrics, orthopaedics, traumatology, physiatrics, occupational medicine and sports medicine (Tuisku et al. 2002a).

2.4.2. Clinical relevance

Developing objective methods to measure various motion characteristics for studying the pathophysiology of movement disorders and their response to treatment is essential (Jankovic and Frost 1981). Certain neuropsychiatric disorders with prominent motor symptoms have been a focus of movement analysis. Objective quantification of the frequency and intensity of tics in Tourette's disorder is considered to be essential for diagnostic purposes, evaluation of treatment response and increasing understanding of the pathophysiology of the disease (Tulen et al. 2001). An accelerometric method has been developed for these purposes (Tulen et al. 2001). Instrumental analysis of the quality of motor activity may sometimes be useful in differentiating between neurological and psychiatric aetiologies for motor symptoms (Knutsson and Martensson 1985). Measuring the diurnal activity and exploring the activity rhythm may aid in subtyping some psychiatric disorders (Teicher 1995).

Elevated activity levels have been detected by accelerometric studies in such psychiatric disorders as ADHD, mania and agitated depression, whereas attenuated activity has been found in bipolar depression and seasonal depression, in which a significant degree of circadian dysregulation appears to be persent (Teicher 1995). The circadian dysregulation is pathophysiologically interesting, as it seems to normalize in seasonal depression during an antidepressive treatment response to bright light therapy (Partonen et al. 1993). Accelerometric studies also show attenuation of circadian rhythm in major depression, and the antidepressant drugs have been hypothesized to work by restoring the circadian rhythm (Teicher 1995). Ambulatory accelerometry has also been validated for quantifying motor activity for the purpose of psychopharmacological studies (Tulen et al. 1997). In elderly schizophrenia patients, a higher dosage of neuroleptics and elevated levels of EP symptoms were associated with flattening of circadian activity rhythm measured by actigraphy (Martin et al. 2001).

The iatrogenic, drug-induced movement disorders have traditionally been evaluated by rating scales, which are based on clinician's subjective judgements (Simpson and Angus 1970, Barnes 1989, Caligiuri 1994, Cunningham Owens 1999) and often fail to

detect small but significant changes in motor function (Jankovic and Frost 1981). Furthermore, some rating scales have unsatisfactory statistical properties (Cunningham Owens 1999, Loonen et al. 2000) or are unsuitable for drug-induced EP symptoms because of their item selection (Cunningham Owens 1999). Measuring motor activity offers a window for objective qualitative and quantitative analyses of EP adverse effects, besides being helpful in diagnosing them. Drug-induced EP symptoms are generally underdiagnosed in clinical practice (Weiden et al. 1987, Hansen et al. 1992). Early detection of motor symptoms also supports identifying concomitant, more hidden and underdiagnosed emotional and cognitive components of EP adverse effects. Early diagnosis and treatment of EP symptoms is important to prevent their chronic development (Cunningham Owens 1999) and harmful clinical effects (Lindström 1994, Newcomer et al. 1994, Owens 1996, Cunningham Owens 1999).

Clinical neurophysiological methods, such as EMG, produce detailed and accurate information on motor activity, but their disadvantage is that they are non-naturalistic and even invasive. In general, what we gain in objectivity and accuracy with instrumental measuring, we lose in relating to the patient's daily life and practical significance. The most naturalistic instrumental assessment methods of motor activity are accelerometric, ambulatory monitors. Because their disturbing effect on normal moving of the subject is minimal and no laboratory assessment is needed, patient compliance is expected to be good and actometric studies cost-effective based on sleep studies (Kazenwadel et al. 1995).

In sleep studies, motor activity is measured to detect pathological movement patterns in legs, quantify overall movement activity during sleep, diagnose sleep disorders and define the sleep stage in polysomnography, examine the circadian rhythm, and grossly differentiate between sleep and wakefulness (Rechtschaffen and Kales 1968, Sadeh et al. 1989, Mills et al. 1993, Sadeh et al. 1995, Chokroverty 2000).

2.4.3. Drug-induced extrapyramidal symptoms

All motor EP symptoms can be measured by objective instruments. Parkinsonian symptoms have been studied more than the others, initially because of the clinical

importance of primary Parkinson's disease. The earliest documented study, in which an electromechanical transducer was used to record rigidity, was reported in 1959 (Caligiuri 1994). Since then, this method has been further developed and applied to neuroleptic-induced EP rigidity (Caligiuri 1994, Caligiuri et al. 1998). In general, the instrumental methods used in primary parkinsonism can be applied to drug-induced parkinsonism. In primary parkinsonism, the transducer has been used to study the motor components of akinesia (Benecke et al. 1986), and actometry has been used to quantify the daily motor activity and detect the increase of activity in response to treatment in hypokinetic patients (Fujikane et al. 1997). Accelerometric methods have been developed to identify and monitor the qualities of parkinsonian tremor (Frost and Jankovic 1981, van Someren et al. 1998).

Neuroleptic-induced tremor has been analysed qualitatively and quantitatively by EMG recording of ankle antagonist muscles (Bathien et al. 1984). It has also been measured with accelerometric applications including tremography (Alpert et al. 1976, Collins et al. 1979, May et al. 1983). When developing neuroleptic-induced tremor, the frequency of the tremor in accelerometry seems to be a more significant pathological sign than the amplitude (Collins et al. 1979), although a decrease of amplitude has been observed in EMG as part of the treatment response to anticholinergic medication (Bathien et al. 1984). Accelerometric decrease of tremor frequency from the level of physiological tremor (10 Hz) seems to be a preceding sign of developing EP symptoms (Collins et al. 1979).

Instrumental methods can also be helpful in differential diagnosis of different types of tremor. In addition to detecting the amplitude and frequency of tremor, accelerometry has been used to analyse the smoothness of motion and the waveform of acceleration during a voluntary movement of a patient with tremor (Jankovic and Frost 1981). Quantitative computerized tremor analysis by EMG and accelerometry have been applied to differentiate between normal physiological tremor and essential tremor (Louis and Pullman 2001) and to monitor long-term age-related changes in tremor frequency (Elble 2000). These tremors of higher frequencies may be difficult to discriminate by instrumental measuring from the postural component of parkinsonian tremor of frequency range 8-10 Hz. The frequency range of clinically well-identified rest-tremor in parkinsonism is, however, lower, 4-6 Hz (Cunningham Owens 1999).

The typical tremor frequency range of parkinsonism (above 4 Hz) is higher, and thus, distinguishable from the frequency range of NIA activity, which is below 4 Hz (Braude et al. 1984, Rapoport et al. 1994, Cunningham et al. 1996).

The lower limb movement patterns in NIA have been studied qualitatively by EMG (Lipinski et al. 1991, Cunningham et al. 1996) and accelerometry (Braude et al. 1984, Rapoport et al. 1994). EMG reveals continuous rhythmic bursts of lower limb activity of 0.5-3 Hz in episodes of 1.7 min in average duration (Lipinski et al. 1991, Walters et al. 1991, Cunningham et al. 1996). An EMG marker of NIA was established when the duration of uninterrupted rhythmic lower limb activity of 0.5-3 Hz exceeded 10 s, and this marker differentiated the NIA patients from neuroleptic-treated patients without NIA with a sensitivity of 69% and a specificity of 70% (Cunningham et al. 1996). The presentation of NIA activity was positively correlated with the relative neuroleptic dose (Cunningham et al. 1996). Rhythmic lower limb activity of frequencies below 4 Hz has also been demonstrated by accelerometry in NIA patients (Braude et al. 1984, Rapoport et al. 1994). Quantification of diurnal motor activity in NIA has been performed by actometry (Gardos et al. 1992, Poyurovsky et al. 2000), demonstrating an overall increase of diurnal motor activity in NIA patients and a trend to specific periodicity (Poyurovsky et al. 2000).

EMG is the most commonly used method in instrumental quantification of TD and other forms of dyskinesia. The most prevalent forms of dyskinesia are the neuroleptic-induced TD, levodopa-induced dyskinesia and dyskinesias related to Huntington's disease (Hoff et al. 1999). EMG activity in TD has been classified into three types: rhythmic clonic (1-3 Hz) and tonic (below 1 Hz) bursts, and irregular bursts of varying length, frequency and amplitude. Unlike in tremor, there is no reciprocal co-ordination between agonist and antagonist muscle activities in TD (Bathien et al. 1984). The spreading, distribution and amplitude of dyskinetic activity has been analysed in detail by a combination of video and EMG recording in levodopa-induced dyskinesia (Marconi et al. 1994). Other objective techniques of quantifying dyskinetic movements include, for example, digital video recording movement analysis, force transducer, photodetectors and ultrasound counter (May et al. 1983, Nilsson et al. 1996, Hoff et al. 1999). The current instrumental methods of assessing TD require a

laboratory setting and provide only a momentary assessment of symptom severity. An accelerometric method for quantification of the spontaneous movements of TD patients has been presented by Fann et al. (1977). The recording sites were both hands, legs and the chin of the patient. Ambulatory accelerometry allowing a naturalistic long-term home-recording has been suggested as a possible solution for these methodological problems (Hoff et al. 1999).

The electromyographical properties of primary dystonia have been studied in detail (Pullman et al. 1996), and an EMG method for quantitative and qualitative evaluation of dystonic muscle has been developed for clinical use (Dressler 2000). One case report outlines the possible usefulness of EMG analysis in differential diagnosis of neuroleptic-induced tardive dystonia (Jyoichi et al. 1989).

A major difficulty in diagnosis and monitoring of EP adverse effects, and thus, also in research and evaluation of new antipsychotic drugs, is that EP symptoms are difficult to measure. Instrumental techniques have been developed for objective evaluation of EP adverse effects, but their impracticality has limited their clinical use (May et al. 1983). The instrumental assessment of pre-existing motor abnormalities has predictive value for the prognosis of developing drug-induced EP symptoms (Collins et al. 1979, Caligiuri et al. 1998). The instrumental measurements of motor activity used in EP symptoms are presented in Table 1.

Table 1: Instrumental techniques of assessing neuroleptic-induced movement disorders and their usefulness.

	Accelerometric methods	**Electromyography**	**Transducer**
Parkinsonism	+++	++	+++
Akathisia	+++	++	-
Dystonias	-	+	-
Tardive dyskinesia	+	++	-

- : not reported
+ : at least one report
++ : several studies: diagnostic significance
+++ : valid for clinical practice: supports diagnostics and monitoring

3. REVIEW

3.1. Neuroleptic-induced akathisia (NIA)

Akathisia is characterized by an unpleasant, distressing inner restlessness, the urge to move and restless movements (Sachdev 1995a, Cunningham Owens 1999). The word ”akathisia” is of Greek origin and literally means ”not to sit”, referring directly to the inability to sit still which has been observed in akathisia patients and is experienced by themselves. Akathisia was first regarded as a non-organic psychiatric disorder before it was mentioned as an organic, EP symptom when described in association with idiopathic and post-encephalitic parkinsonism in 1923 (Adler et al. 1989, Sachdev 1995a). Akathisia is estimated to be present in 25-50% of patients with idiopathic Parkinson’s disease in the absence of neuroleptic medication (Lang and Johnson 1987, Witjas et al. 2002). The first case of drug-induced akathisia (DIA) was reported in 1947 as an adverse effect of promethazine (Sachdev 1995a, Chung and Chiu 1996). After the invention of neuroleptic drugs, the term akathisia has come to be used synonymously with drug-induced akathisia (DIA) (Sachdev 1995). The

prevalence of akathisia is about 20-30% in patients on long-term neuroleptic treatment, but the current incidence is expected to be lower than in the past, as more atypical (novel) antipsychotics are used first-line (Chung and Chiu 1996).

The drugs most frequently implicated in the pathogenesis of akathisia are those which either directly or indirectly interfere with dopaminergic functions, and it is reasonable to conclude that this is a fundamental mechanism underlying development of the disorder (Cunningham Owens 1999). DIA is best known as an important EP adverse effect of D2 blocking conventional antipsychotics, but several other drugs with antidopaminergic activity also exist which can cause acute DIA, for example, lithium, buspirone, calcium channel antagonists (Sachdev 1994) and antiemetics (Ganzini et al. 1993, Foster et al. 1996). Pharmacological studies suggest that the serotonergic, adrenergic and opioid systems are involved in the pathophysiology of akathisia, either directly or through the dopamine system (Chung and Chiu 1996). DIA caused by selective serotonin reuptake inhibitors may be related to an inhibitory effect of serotonergic input to dopaminergic systems (Leo 1996). A noradrenergic mechanism is supported by the observations of Zubenko et al. (1987), who reported akathisia induced by tricyclic antidepressants and relieved by a beta-adrenergic blocker, propranolol. DIA may be involved in the pathophysiological mechanisms of suicidal ideation and behaviour precipitated by antidepressive drugs (Teicher et al. 1993).

Neuroleptic-induced akathisia (NIA) is a common but underdiagnosed and easily misdiagnosed adverse effect of conventional antipsychotics (Barnes and McPhillips 1999). Early diagnosis is essential because akathisia often causes marked distress to the patient and may progress, become chronic or be related to a higher risk of developing tardive dyskinesia (Munetz and Cornes 1983). It may also predispose to physical aggression and threatening behaviour (Ratey and Gordon 1993, Stubbs et al. 2000), suicidal behaviour (Drake and Ehrlich 1985, Siris 2001), insomnia (Goldstein 2000), poor drug compliance (Van Putten 1974, Lindström 1994, Goldstein 2000), poor treatment response (Newcomer et al. 1994) and exacerbations of psychosis (Van Putten 1975). Furthermore, there is some evidence of the disruptive effect of NIA on spatial working memory, which is probably mediated by the increased distractability in NIA (McCartan et al. 2001).

The lower risk of developing akathisia and other EP symptoms with novel antipsychotics than with conventional antipsychotics (Miller et al. 1998, Goldstein 2000, Voruganti et al. 2000) is hypothesized to be related to the lower D2 receptor occupancy with commensurately higher 5-HT2 occupancy and limbic selectivity (Arnt and Skarsfeldt 1998, Goldstein 2000) of novel antipsychotics. In addition to these common features, most novel antipsychotics have high relative affinity for D1 receptors, alpha 2 adrenoreceptors and histamine 1 receptors (Arnt and Skarsfeldt 1998). Fewer EP adverse effects with clozapine and quetiapine may be due to loose binding of these drugs at D2 receptors, while risperidone and olanzapine may cause EP symptoms at higher doses (Goldstein 2000). In comparison, risperidone produces EP symptom levels intermediate between clozapine and conventional antipsychotics (Arnt and Skarsfeldt 1998, Miller et al. 1998), and higher than olanzapine (Tran et al. 1997, Arnt and Skarsfeldt 1998, Bobes et al. 2002). The EP adverse effect of risperidone, however, is highly dose-dependent; at higher dosages, the risk appears to be equal to that of conventional antipsychotics, while at lowest treatment dosages, the risk is reported to be relatively low (Tarsy et al. 2002).

Positron emission tomography (PET) findings indicate that neuroleptic-induced EP syndromes, including NIA, are related to the degree of neuroleptic D2 receptor occupancy in the nucleus caudatus and nucleus putamen of the basal ganglia (Farde et al. 1992). The theory concerning involvement of mesocortical dopaminergic tracts in pathophysiology of NIA is mainly supported by animal studies (Marsden and Jenner 1980, Cunningham Owens 1999). While the blockade of D receptors in the striatum produces inhibition of locomotor activity, the reverse occurs on blockade of mesocortical dopaminergic systems, supporting their role in the pathogenesis of the hyperkinetic symptoms of akathisia (Marsden and Jenner 1980). Some limbic cortical structures involved in the pathophysiology of NIA according to an immunohistochemical animal study (Ohashi et al. 1998) can have a central role in mediating the subjective dysphoria related to akathisia.

The recommended initial interventions to treat NIA are dose reduction of the antipsychotic medication or switching it to another; the most recommended atypical antipsychotics are clozapine, olanzapine and quetiapine (Taylor et al. 2001). When this is not effective or possible, either betablocker (propranolol) or an anticholinergic

drug is added to the treatment, but the latter may be effective only in patients with comorbid drug-induced parkinsonian symptoms (Fleischhacker et al. 1990, American Psychiatric Association 1997, Taylor et al. 2001). Propranolol is suggested to be the most effective treatment according to research data, but comparisons between treatment options are still needed (Adler et al. 1989, Fleischhacker et al.1990, American Psychiatric Association 1997, Poyurovsky and Weizman 2001). Secondary options include benzodiazepines, cyproheptadine and clonidine (Taylor et al. 2001). Also low-dose mianserine has proved effective in treatment of NIA. The treatment response is probably mediated by increase of the 5-HT2/D2 receptor occupancy ratio (Poyurovsky et al. 1999). Other serotonergic agents may prove useful in the future (Poyurovsky and Weizman 2001).

NIA and other EP adverse effects can be prevented by choosing atypical antipsychotics, by careful patient monitoring and adequate patient information, and by encouraging patients to report subjective experiences of adverse effects. EP adverse effects are among the most important reasons for non-compliance, causing subjective suffering, lowering of function level and social stigma (Lindström 1994, Owens 1996). Despite the increasing amount of atypical antipsychotics available, EP symptoms still threaten the treatment of psychosis because: 1. Even atypical neuroleptics may cause EP symptoms (Miller et al. 1998, Barnes and McPhillips 1999, Tarsy et al. 2002), especially akathisia, which is associated with a worse clinical outcome (Cohen et al. 1991) and 2. The clinicians' ability to identify these adverse effects is generally poor, varying between 10% and 59% (Weiden et al. 1987, Hansen et al. 1992).

The diagnostic criteria for acute NIA are described in DSM-IV (Table 2). DIA is classified into acute, chronic, tardive and withdrawal akathisia (Sachdev 1995a, 1995b). Special subtypes of DIA described in the literature, such as subjective akathisia (Van Putten and Marder 1986) and hypokinetic akathisia (Tuisku et al. 2000), are difficult to diagnose and sometimes impossible to assess by the most established rating scale, the Barnes Akathisia Rating Scale (BARS), which disregards the richness of clinical features (Cunningham Owens 1999). Differential diagnosis of DIA includes other types of akathisia like idiopathic akathisia, akathisia related to Parkinson's disease, secondary akathisia related to head injury and pseudoakathisia,

suggested to be a variant of tardive dyskinesia rather than a form of akathisia (Stahl 1985).

NIA differs from TD by a prominent inner sense of discomfort, the voluntary nature of movements, earlier onset in the course of neuroleptic treatment and non-involvement of the perioral area in contrast to TD (Munetz and Cornes 1983). A tardive form of NIA has also been described in which movements may be more stereotyped than in acute NIA (Sachdev 1994). Tardive akathisia (TA) is associated with neuropsychological deficits and negative symptoms in schizophrenia patients even more strongly than TD (Sachdev et al. 1996). TD often co-occurs with TA (Sachdev 1994) or chronic NIA (Barnes and Braude 1985), but the relationship between TD and TA is unclear (Sachdev et al. 1996). Although a causality or a successive continuum of symptoms has been suggested to exist between them, no evidence exists of interrelatedness between these disorders (Kahn et al. 1992). TD is differentiated from TA by less subjective awareness and control over motor symptoms, which are more purposeful in the latter (Sachdev 1994, American Psychiatric Association 2000).

The most characteristic diagnostic sign for both acute and chronic akathisia is the subjective experience of an inability to keep the legs still. It is more specific to NIA than an overall sense of inner restlessness, which is also quite common in psychiatric patients without NIA and seems to diminish or disappear in chronic NIA (Barnes and Braude 1985). Differential diagnosis of akathisia is often difficult, and several other hyperkinetic states and disorders with psychomotor agitation have to be considered including psychotic agitation related to schizophrenia, agitation related to mood disorders, generalized anxiety, substance intoxication and -withdrawal syndromes, ADHD and RLS (American Psychiatric Association 2000).

3.2. RLS

Ekbom (1944) described an idiopathic syndrome, “Asthenia crurum paraesthetica”, referring to previous descriptions of “anxietas tibiarum”, which he later renamed “Restless legs syndrome” (1945, 1960). He described unpleasant lower limb paresthesias, “creeping or crawling” sensations elicited by sitting or lying down,

which cause an urge to move the legs or an inability to keep them still. The symptoms are mostly present in the evening and night-time and are relieved by moving the legs. Emotions do not seem to play a large role in RLS according to Ekbom's original descriptions.

RLS is a common, sometimes disabling and often misdiagnosed condition (IRLSSG 1995), with both subjective sensations and objective motor symptoms (Montplaisir et al. 2000). The distressing subjective sensations may be present and incapacitating during the daytime, but the symptoms typically worsen at night, often leading to insomnia (Ekbom 1960, Montplaisir et al. 2000, Bassetti et al. 2001). Another harmful consequence of RLS is secondary depression (Trenkwalder et al. 1999b, Ulfberg et al. 2001a), which may affect one-third of these patients during their lifetime (Bassetti et al. 2001). Based on comorbidity findings, Pichietti et al. (1999) suggest that RLS may indirectly, through sleep disruption, lead to attention deficit hyperactivity disorder. RLS is considered to be both a sleep disorder and a movement disorder (Hening et al. 1999a, Amar 2001).

The International Restless Legs Syndrome Study Group (IRLSSG 1995) has defined the diagnostic criteria for RLS (Table 2). Two of the essential diagnostic criteria of RLS, namely, "occurring with rest" and "during the night", can be speculated to have a causal relationship, but actually they seem to be independent phenomena based on diurnal rest-activity and other symptom severity measurements (Hening et al. 1999b, Trenkwalder et al. 1999a). The differential diagnostic disorders to be considered are NIA (see section 3.5.1.), isolated periodic limb movement disorder without RLS, painful legs and moving toes syndrome, nocturnal leg cramps, restless insomnia, neuropathic pain syndromes, arthritis, anxiety syndromes, ADHD and other hyperactivity states such as hyperthyroidism and Tourette's disorder (Montplaisir et al. 2000, Allen and Earley 2001, Tan and Ondo 2001).

The motor and sensory symptoms of RLS are typically localized to the lower limbs, but the upper limbs may also be involved (Bassetti et al. 2001). The motor hyperactivity of RLS patients during immobilization seems to consist of both short-lasting, involuntary periodic leg movements (PLM) and more prolonged voluntary movements made by the patient to get rid of discomfort (Montplaisir et al. 1998).

EMG recording during an immobilization test has been developed to measure symptom severity (Montplaisir et al. 1998). As most of the RLS patients exhibit PLM in EMG, the PLM index is often used to support a diagnosis of RLS (Montplaisir et al. 1998) and to monitor the severity of symptoms (Montplaisir et al. 1999). The periodic limb movement disorder (PLMD), however, is a distinct disorder, not always present in RLS (Allen and Earley 2001), including severe cases (Montplaisir et al. 1997). Furthermore, it is a non-sensitive marker of RLS (Montplaisir et al. 1998).

The prevalence of idiopathic RLS is estimated to be around 5% in the general population and to be age-related (Chokroverty and Jankovic 1999). According to an epidemiological questionnaire, frequent restless legs symptoms are reported by 3% of people aged 18-29 years, by 10% of those aged 30-79 years and by 19% of those aged over 79 years. Somatic reasons for symptoms were not excluded in this study (Phillips et al. 2000). Family history is estimated to be present in one-third to two-thirds of RLS patients and an autosomal dominant model of inheritance has been suspected (Chokroverty and Jankovic 1999, Lazzarini et al. 1999). A positive family history is more frequent in idiopathic RLS than in secondary RLS (Winkelmann et al. 2000). The hereditary form of RLS presents with clinical symptoms similar to the non-hereditary form but has an earlier onset (Winkelmann et al. 2000). Recent findings concerning genetic penetrance suggest a heterogenic genetic aetiology (Lazzarini et al. 1999), and some evidence for a recessive mode of inheritance has been found in a linkage study of one family (Desaultes et al. 2001).

Secondary RLS may be related to Parkinson's disease, neuropathy, uremia, iron deficiency, pregnancy and rheumatoid arthritis (Goodman et al. 1988, Salih et al. 1994, Chokroverty and Jankovic 1999, Stocchi et al. 2000, Allen and Earley 2001). Primary, idiopathic RLS (sporadic or genetic) may be difficult to differentiate from secondary RLS (Chokroverty and Jankovic 1999), and the categorization between primary and secondary forms of RLS may sometimes be unclear since axonal neuropathy (Iannaccone et al. 1995) and abnormally low serum iron levels (Aul et al. 1998) seem to be common subclinical findings in primary RLS. After findings of slight peripheral axonal neuropathy in each patient of a study sample, the previous diagnosis of "primary" RLS for these patients may be questioned (Iannaccone et al. 1995). Low serum ferritine level, an indicator of iron deficiency is correlated with

subjective RLS symptom severity and decreased sleep efficiency but not with number of PLMS (Sun et al. 1998).

A defect in iron metabolism has been suggested to be involved in the pathophysiology of RLS, as iron is a component of the D2 and μ-opiate receptors (Aul et al. 1998), which seem to have central roles in the pathophysiological mechanisms according to pharmacological studies (Chokroverty and Jankovic 1999). There is evidence of treatment response both to dopaminergic drugs (von Scheele 1986, Kaplan et al. 1993, Earley et al. 1998) and to opioids (Hening et al. 1986, Lauerma and Markkula 1999), but the response to opioids can be inhibited by antidopaminergics (Montplaisir et al. 1991), which further supports the dopaminergic model as the primary pathophysiological mechanism in RLS (Earley et al. 2001).

A PET study (Turjanski et al. 1999) reveals reduced striatal dopaminergic function in symptomatic RLS patients. Another PET study shows the same finding in RLS patients with PLM disorder (Ruottinen et al. 2000). The dopaminergic abnormalities in the basal ganglia of RLS patients seem to be functional, rather than neurodegenerative, because they were not found in the basal ganglia of RLS patients in an asymptomatic phase (Trenkwalder et al. 1999c). The intracortical inhibition measured by transcranial magnetic stimulation (TMS) is apparently reduced in RLS. The TMS findings suggest that the functional pathology is a subcortical rather than a primary cortical or corticomuscular phenomenon (Tergau et al. 1999).

To date, dopaminergic drugs are the best studied and most effective agents for treatment of RLS (Chesson et al. 1999). The largest number of studies have been conducted on levodopa compounded with carbidopa or benserazide, but rebound restlessness is often a clinical problem in these treatments (Hening et al. 1999a, Montplaisir et al. 1999). In any case, treatment with dopamine agonists may be more effective (Hening et al. 1999a). Among dopamine agonists, bromocriptine and pergolide are associated with adverse effects that limit their clinical usefulness, but pramipexole has proved to be both safe and a potent therapeutic agent for RLS (Montplaisir et al. 1999).

3.3. ADHD in antisocial personality disorder (ASP)

ADHD is the most common psychiatric disorder of childhood, affecting approximately 5% of school-aged children (Szatmari 1992), but in adolescents and adults the prevalence is much lower (Cuffe et al. 2001). The combined type of ADHD fulfills both the criteria for attention deficit as well as for hyperactivity and impulsiveness, whereas the subtypes (predominantly inattentive and predominantly hyperactive type) do not fulfill the criteria for both symptom dimensions (American Psychiatric Association 2000) (Table 2). Prospective longitudinal studies show that part of the childhood onset ADHD symptoms persists in nearly half of the subjects until adolescence or early adulthood and that ADHD is a risk factor for conduct disorder, ASP and substance abuse (Gittelman et al. 1985, Mannuzza et al. 1993). ADHD and conduct disorder share a common genetic aetiology, and ADHD with a comorbid conduct disorder seems to be a more severe variant of ADHD (Thapar et al. 2001) and to have a worse prognosis (Taylor 1999) than ADHD alone. Taylor (1999) integrates his own findings and evidence from other studies with a psychological approach in concluding that ADHD is a biological and psychosocial risk factor for conduct disorder, which is likely to develop in ADHD children of dysfunctional families. Conduct disorder, by contrast, does not predispose to ADHD.

A history of ADHD is commonly found in subjects with ASP, and ADHD is considered to be one of the precursors of ASP in the presence of conduct disorder (McCracken et al. 2000). The diagnostic criteria of ASP include more or less learned social features and some seemingly more biological aspects of behaviour, such as aggressiveness and impulsiveness, the latter of which is also a diagnostic feature of ADHD (American Psychiatric Association 2000). Shared neurobiological features appear to be present in ASP and ADHD (Renfrew 1997). A reduction in aggression with psychostimulants may result from enhanced attention and intellectual functions or from a reduction in impulsiveness (Renfrew 1997, Cherek and Lane 2000). The response of aggressiveness to psychostimulants supports the role of D in regulation of aggressiveness among other transmitters including NA, 5-HT and ACh (Renfrew 1997).

The central pathophysiological theory of hypodopaminergic aetiology in ADHD arises from the therapeutic effect of psychostimulants (Seeman and Madras 1998) and is supported by dopamine-related candidate gene findings (Thapar et al. 1999). The mode of inheritance seems to be polygenic in ADHD, and interactions between serotonergic and dopaminergic neurotransmitter systems are involved in the pathophysiology (Quist and Kennedy 2001). The central role of dopaminergic circuits in the pathophysiology of ADHD is further supported by findings of striatal hypoperfusion in ADHD (Lou et al. 1989). A developmental defect in frontostriatal circuits has been suggested to be one of the pathophysiological mechanisms (Toft 1999). The frontostriatal dopaminergic deficit has gained growing evidence as a central pathophysiological mechanism of ADHD affecting inhibition and working memory (Lewy and Swanson 2001).

The recommended primary pharmacological treatment options based on research evidence in ADHD are the psychostimulants methylphenidate and dextroamphetamine. The use of pemoline is limited because of reported liver toxicity. Other, secondary options include antidepressants and clonidine, which reduces the autonomic sympathicotonia by activating central alpha-2 adrenergic receptors. Clonidine can be used to treat comorbid aggressive symptoms and tics in ADHD. (Pliszka et al. 2000).

3.4. Asperger's disorder

Asperger's disorder is a disorder in the autism spectrum. The syndrome now called Asperger's disorder is retrospectively assumed to have been first described using the label "schizoid personality disorder" (Gillberg 1998a), showing a possible diagnostic overlap between schizophrenia spectrum and autism spectrum disorders, especially concerning Asperger's disorder or high-functioning autism and childhood-onset schizophrenia (Gillberg 1998b). More long-term follow-up studies are needed before high-functioning autism and Asperger's disorder can be concluded to be different disorders (Gillberg 1998a). This new diagnostic concept of Asperger's disorder, still under some debate (Volkmar et al. 2000), indicates a syndrome characterized by altered social interactions, restricted interests and repetitive, stereotyped behaviour, as

in autism, but different from the latter in that it does not display any significant delay in acquisition of language, psychomotor and cognitive skills (Table 2).

The prevalence of autism spectrum disorders, including childhood autism, Asperger's syndrome, disintegrative disorder and atypical autism, is estimated to be at least 4-5 per 1000 children. Asperger's syndrome occurs at a minimum rate of 26-36 in 10 000 children (Gillberg and Wing 1999). Autism spectrum disorders are probably caused by the interaction of several mutant genes, which are likely to be located on different chromosomes (Gillberg 1998c).

Because of the scarcity of reports on neuroanatomical and neurochemical findings in Asperger's disorder, it is necessary to rely on studies of autistic patients in order to elaborate physiopathological hypotheses (Godbout et al. 2000). Computed tomography demonstrates a reduced density of the caudate nucleus (Jacobson et al. 1988), and PET reveals presynaptic, prefrontal hypodopaminergia in autism (Ernst et al. 1997). Obvious hypofunction in the midbrain dopaminergic neurons of autistic children may lead to secondary dopaminergic hypersensitivity (Segawa and Nomura 1992). Primary dopaminergic dysfunction and structural abnormalities in the basal ganglia may explain the vulnerability to neuroleptic-induced EP symptoms in autistic patients (Campbell et al. 1997).

Movement disorders are common in Asperger's disorder, manifesting clinically as clumsiness (Gillberg 1995, Smith 2000, Weimer et al. 2001), lack of motor co-ordination (Miyahara et al. 1997) and stereotypic, repetitive movements (Ringman and Jankovic 2000). The clumsiness and motor inco-ordination observed in Asperger's disorder patients are probably related to a proprioceptive deficit (Weimer et al. 2001). In addition to these typical motor disorders, patients may suffer from other motor disorders associated with comorbid disorders such as Tourette's disorder (Kadesjö and Gillberg 2000) and ADHD (Ghaziuddin et al. 1998). Moreover, attention deficit symptoms not fulfilling the diagnostic criteria of ADHD are very common in disorders in the autism spectrum. Both motor hyperactivity and hypoactivity are encountered in autism (Gillberg and Billstedt 2000). Other psychiatric disorders showing comorbidity with Asperger's disorder are affective,

anxiety and obsessional disorders, psychoses and antisocial behaviour (Green et al. 2000).

The existence of true comorbidity between Asperger's disorder, Tourette's disorder and OCD may be questioned because of the overlapping features of these disorders (Gillberg 1998a). The comorbidity with externalizing disorders may be partially explained by the primary difficulties in social perception, leading to irritability and impulsivity, but according to clinical research data, a simple association between the level of social impairment in Asperger's disorder and the degree of psychiatric comorbidity has not been found (Green et al. 2000). The comorbidity and overlapping features between these disorders may be due to a common developmental defect in frontostriatal circuits (Gillberg 1998a), predisposing to a broad spectrum of neuropsychiatric symptoms modulated individually by genes and environmental factors.

The pharmacological treatment of Asperger's disorder may be focused on autistic symptoms or on current disturbing secondary symptoms, such as aggressive behaviour and hyperactivity, but use of pharmacological interventions is limited by adverse effects (Nyden et al. 2000). Because pharmacotherapy is unlikely to alter most core features of autism, including impairments in communication, social interaction, stereotyped behaviour and a narrow focus of preoccupation, the more usual targets for treatment are the secondary symptoms or comorbid disorders (Arnold et al. 2000). Antidopaminergic, antiserotonergic, serotonine re-uptake inhibiting, opiate antagonist and dopamine agonist drugs have been explored in treatment of autistic disorders, among which haloperidol has been studied most systematically. Most of these drugs reduce hyperactivity symptoms and haloperidol seems to be effective in treating disruptive symptoms (Campbell and Cueva 1995). Antipsychotics have been used cautiously in autistic disorders because of EP adverse effects (Scahill and Koenig 1999). The high rate of baseline motor abnormalities implicates careful screening and monitoring of movement disorders during treatment (Campbell et al 1997). The serotonin re-uptake inhibiting effect may be effictive in treating core symptoms of autism, while noradrenaline re-uptake inhibition is useful in treating comorbid ADHD

symptoms (Hollander et al. 2000). Valproate may be beneficial in treating affective instability, impulsiveness and aggressive behaviour (Hollander et al. 2001).

3.5. Common features

3.5.1. Clinical and diagnostic

In the literature, the descriptions of RLS are often intermixed with those of akathisia (Adler et al. 1989, Sachdev 1995a). Blom and Ekbom (1961) noted a clinical similarity between RLS, earlier described by Ekbom (1944, 1960), and NIA, but they also remarked that NIA symptoms, unlike restless legs symptoms, were present during the daytime and did not disturb sleep. Furthermore, they described paresthesias and restlessness to be confined to the legs in RLS, whereas in NIA the restlessness may be more generalized.

The question has arisen whether NIA is a form of RLS (IRLSSG 1995) as they share some diagnostic (Table 2), clinical and polysomnographic features (Walters et al.1991, Allen and Earley 2001). Several differences have, however, been described: more localization of symptoms in the lower limbs and more pronounced dysesthesia in RLS, worsening or triggering of the symptoms in a lying position in RLS, different circadian distribution of the symptoms, more disturbed sleep pattern and more PLMS in RLS (Walters et al. 1991, Sachdev 1994, Chokroverty and Jankovic 1999, Montplaisir et al. 2000, Allen and Earley 2001). Furthermore, the urge to move in akathisia is more often generated by an inner sense of restlessness than by specific lower limb sensations typical of RLS (Walters et al. 1991, IRLSSG 1995). Akathisia related to Parkinson's disease or other organic brain diseases has not been fully characterized (Sachdev 1995a), but NIA is defined by diagnostic criteria in DSM-IV (American Psychiatric Association 2000) and is distinguishable from RLS by its aetiology

Table 2: DIAGNOSTIC CRITERIA OF SELECTED NEUROPSYCHIATRIC DISORDERS

I. Neuroleptic-induced acute akathisia (NIA)

A. Development of subjective complaints of restlessness after exposure to a neuroleptic medication.
B. At least one of the following observed: (1) fidgeting movements or swinging of the legs, (2) rocking from foot to foot while standing, (3) pacing to relieve restlessness, (4) inability to sit still for at least several minutes.
C. Onset of symptoms in A and B occurs within 4 weeks of initiating or increasing the dose of the neuroleptic, or of reducing medication used to treat acute extrapyramidal symptoms.
D. Symptoms in A are not better accounted for by a mental disorder.
E. Symptoms in A are not due to a non-neuroleptic substance or to a neurological or other general medical condition.
(DSM-IV, American Psychiatric Association 2000)

II. Restless legs syndrome (RLS)

Essential features:

A. Desire to move the limbs usually associated with paresthesias or dysesthesias.
B. Motor restlessness.
C. Symptoms are worse or exclusively present at rest with at least partial or temporary relief with activity.
D. Symptoms are worse during the evening or at night.
(IRLSSG, 1995)

III. Attention deficit hyperactivity disorder (ADHD)

A. Either six or more symptoms of inattention, or six or more symptoms of hyperactivity-impulsivity (e.g. fidgeting with hands or feet or squirming in seat, leaving situations in which remaining seated is expected, running or climbing in inappropriate situations).
B. Some symptoms that caused impairment were present before the age of 7 years.
C. Some impairment from the symptoms is present in two or more settings.
D. Clear evidence of clinically significant impairment in social, academic or occupational functioning.
E. Symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or another psychotic disorder and are not better accounted for by another mental disorder.
(DSM-IV, American Psychiatric Association 2000)

IV. Asperger's disorder

A. Qualitative impairment in social interaction
B. Restricted repetitive and stereotyped patterns of behaviour, interests and activities (e.g. stereotyped and repetitive motor mannerisms).
C. The disturbance causes clinically significant impairment in social, occupational or other important areas of functioning.
D. No clinically significant delay in language.
E. No clinically significant delay in cognitive development, age-appropriate self-help skills, adaptive behaviour or curiousity about the environment.
F. Criteria are not met for another specific pervasive developmental disorder or schizophrenia.
(DSM-IV, American Psychiatric Association 2000)

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Antidepressants have been suggested to be an aetiological factor for both akathisia (Zubenko et al. 1987) and RLS (Markkula and Lauerma 1997), which complicates the differential diagnosis. Actually, the clinical picture of akathisia cases described by Zubenko et al. (1987) also comprises features typical of RLS, such as worsening of symptoms when going to sleep and difficulties in falling asleep because of uncomfortable leg sensations.

Motor restlessness is an essential diagnostic feature of NIA, RLS and ADHD (Table 2). In ADHD, two items in the diagnostic criteria are similar to NIA symptoms: fidgeting with feet while seated and inability to remain seated (Table 2). Both akathisia and ADHD are related to aggressive behaviour (Ratey and Gordon 1993). There is comorbidity and overlapping features between Asperger's disorder and ADHD (Ghaziuddin et al. 1998, Gillberg 1998a) and the under-diagnosis of these developmental disorders in childhood may lead to externalizing behaviour problems and impaired adaptation to society (Nyden et al. 2000). Motor restlessness may also manifest in autistic disorders, among other motor abnormalities (Gillberg and Bilstedt 2000), such as repetitive motor mannerisms typical of Asperger's disorder (Table 2).

3.5.2. Pathophysiological

PET findings of striatal dopaminergic hypofunction have been made in the caudatum and putamen areas in NIA (Farde et al. 1992) and RLS (Turjanski et al. 1999, Ruottinen et al. 2000), and are iatrogenic in NIA. Striatal dopaminergic deficit in ADHD has gained evidence from dopamine transporter findings in brain imaging and genetic studies (Thapar et al. 1999, Krause et al. 2000). Prefrontal hypodopaminergia has been demonstrated in autism by PET (Ernst et al. 1997), and increasing evidence exists of frontostriatal dysfunction in both autistim and ADHD (Gillberg 1998a).

Attempts have been made to explain the familial comorbidity between RLS and ADHD by hypodopaminergic pathophysiology, a common genetic basis for these disorders or a causality related to RLS-induced sleep disruption (Picchietti et al. 1999).

3.5.3. Pharmacological

The beta-adrenergic blocking agent, propranolol, an effective treatment option in NIA (Adler et al. 1989, Poyurovsky and Weizman 2001), is also reported to reduce aggressive symptoms related to ADHD (Mattes 1990).

Clonidine, which has anti-adrenergic and anti-aggressive properties, is a secondary treatment option for both NIA (Adler et al. 1987, Miller and Fleischhacker 2000, Taylor et al. 2001) and ADHD (Pliszka et al. 2000). The hyperactivity and irritability symptoms in autism are also reported to respond to clonidine (Fankhauser et al. 1992, Jaselskis et al. 1992).

Surprisingly, some of the core autistic symptoms can be relieved by psychostimulant treatment focused on comorbid ADHD in autism (Handen et al. 2000). The psychostimulant treatment increases the striatal dopaminergic transmission by blocking the D transporter or by releasing D into the synaptic cleft (Seeman and Madras 1998, Krause et al. 2000).

3.6. Accelerometric studies on selected disorders

Accelerometric methods (see section 2.4.) measure locomotor activity by ambulatory activity monitors. In activity monitors, there are three principal modes of data collection known as “time above threshold”, “zero-crossing” and “digital integration”. In the first one, the monitor tracks the length of time that elapses from the point when acceleration exceeds a threshold value until it falls below the threshold. In the second mode, the monitor detects the number of times that acceleration crosses the zero point within a certain time period. In digital integration, the amount of acceleration is recorded and sampled at a high rate, and these values are used to calculate the average activity level within a time window (Gorny and Allen 1999). All the accelerometric monitors measure locomotor activity quantitatively, and some of them also allow qualitative motion analysis. The smaller the time window, the higher the time resolution of the movement.

Altered locomotor activity is an important sign of several psychiatric disorders (Teicher 1995), whereas specific motor disturbances in psychiatric disorders are obvious clinical signs of organic aetiology in the brain (Beier 1997). An increasing amount of data on accelerometric studies in psychiatry has been collected, and activity monitoring has been suggested to be a valuable research tool of potential aid to clinicians in diagnosis and prediction of treatment response (Teicher 1995). The customary use of accelerometric activity monitoring is diurnal recording with a relatively long time window ranging between several minutes and one hour. In diurnal activity monitoring, the monitors have typically been attached to the non-dominant wrist. However, such movement disorders as NIA and RLS are better manifested in the lower limbs than anywhere else. Gardos et al. (1992) and Mills et al. (1993) have created new methods of quantifying lower limb activity in these disorders.

3.6.1. NIA

Gardos et al. (1992) measured diurnal motor activity in NIA from the non-dominant ankle, comparing patients of different diagnostic categories with or without NIA and a group of healthy controls. The activity appeared to be influenced by both NIA and the psychiatric diagnosis. The diurnal activity seemed to be more related to psychiatric diagnosis than NIA, because manic patients and healthy controls were the most active in diurnal measuring. However, within the group of schizophrenics, NIA had an increasing effect on daytime motor activity. The positive correlation between NIA severity rating and daytime activity level was statistically significant. Poyurovsky et al. (2000) recorded the diurnal activity of schizophrenic patients from the non-dominant wrist, comparing patients with NIA and those without; he observed a higher level of diurnal motor activity in NIA patients. No difference in quantitative activity during sleeping hours was found between the groups.

In addition to quantitative studies, qualitative motion analysis has been performed in NIA. Accelerometric findings of a rhythmic, 0.5-3 Hz lower limb movement pattern in NIA (Braude et al. 1984, Rapoport et al. 1994) are consistent with the results of EMG studies (Cunningham et al. 1996). Abnormal, periodic movement patterns of a constant waveform, frequency and amplitude are reproducible accelerometric findings in NIA (Rapoport et al. 1994).

3.6.2. RLS

In RLS, motor activity is more often recorded by EMG than by accelerometric methods. In sleep studies, the role of ambulatory activity monitoring has traditionally been in differentiation between sleep and wakefulness. Sadeh et al. (1989) validated wrist actometry for this purpose. Mills et al. (1993) examined the usefulness of actometry for objectively assessing motor RLS symptoms with bilateral leg activity monitors to find a time-saving and cost-effective alternative to polysomnography. The quantitative assessment of lower limb activity showed the treatment response in parallel with other symptom severity measures. Later, actometry was validated by Kazenwadel et al. (1995) and utilized in sleep studies (Trenkwalder et al. 1995, Collado-Seidel et al. 1999) as a method comparable to EMG in assessment of PLM. Actometry has also been used to measure quantitative motor activity as a marker of symptom severity in examining the circadian rhythm of RLS (Hening et al. 1999b).

3.6.3. ADHD

Increased diurnal activity in ADHD has been quantified by waist-worn activity monitors. The increase of diurnal activity differentiated hyperactive boys from controls as well as a standardized measure of attention (Porrino et al. 1983a). Diurnal actometric recording from the non-dominant wrist revealed an equal hyperactivity in predominantly inattentive and combined ADHD subtypes (Dane et al. 2000). Hyperactivity in actometry is a more discriminative feature of ADHD than inattention and dyscontrol in psychometric test battery (Halperin et al. 1992). In actometric studies, hyperactivity seems to be related to situations demanding self-regulation (Dane et al. 2000), and motor activity measured during a cognitive task, for example, is a good measure of symptom severity (Reichenbach et al. 1992). In fact, the diurnal hyperactivity of children with ADHD appears to be due more to the relative absence of quiescent periods than to the presence of extremely active periods. This is consistent with the actometric finding that the increase of activity in ADHD children compared with controls is most prominent during academic school activities while sitting in the classroom (Porrino et al. 1983a), and with the clinical observation of difficulties in sitting still (Teicher 1995).

3.6.4. ASP

Diurnal activity has been studied in violent ASP patients by actometric recording from the non-dominant wrist. The patients demonstrated an overall increase of diurnal activity, which was expected to be related to the common history of ADHD in these patients. In a subgroup of antisocial violent offenders with intermittent explosive disorder, the day and night activity levels were indistinguishable, indicating a desynchronized diurnal rhythm (Virkkunen et al. 1994).

3.6.5. Asperger's disorder

In Asperger's disorder, no studies are yet available using accelerometric methods despite the prominent motor symptoms and abnormal levels of motor activity in this disorder. However, the sleep patterns of autistic children have been studied by diurnal actometric recording with a wrist monitor (Hering et al. 1999).

4. RATIONALE, HYPOTHESES AND PURPOSES OF EACH STUDY

Motor restlessness, which can be a manifestation of many underlying disorders, is often poorly recognized and underdiagnosed in clinical practice and probably too often simply attributed to anxiety. Early diagnosis allows proper treatment of hyperactivity states, and thus, careful evaluation and differential diagnostics are required. The two major conditions to consider in patients who present with motor restlessness are NIA and RLS. In addition, ADHD and other neuropsychiatric disorders should be taken into account (Tan and Ondo 2001).

These studies aimed to offer a window to understanding the role of motor abnormality in neuropsychiatric disorders and to bring an objective and simple method for motor assessment into clinical neuropsychiatry. Accelerometric-based actometry offers an objective and naturalistic method for both quantitative and qualitative studies of rest-activity. Actometry has been hailed by Teicher (1995) as an important research tool in clinical psychiatry. It is non-invasive and does not disturb the normal moving of the subject.

The hypothesis of these studies was that measuring motor activity during rest (sitting) by three-channel actometry in a standardized setting would yield abnormal quantitative and qualitative results and would enable characteristic motor features of NIA, RLS, ADHD in ASP and Asperger's disorder to be uncovered.

General purposes of these four studies were to develop a standardized actometric method for diagnostics and monitoring of motor symptoms in neuropsychiatric disorders and to identify characteristic motor signs in NIA, RLS, ADHD and Asperger's disorder.

4.1. NIA study

The assessment and monitoring of NIA rely on rating scales, which are typically based on the clinicians' subjective judgements (Jankovic and Frost 1981, Cunningham Owens 1999). A need exists to develop new, objective methods for diagnostics and to reliably assess symptom severity in this harmful and underdiagnosed adverse effect of antipsychotic drugs. This need for objective methods for identification of NIA has prompted attempts to establish physiological correlates for NIA (Poyurovsky et al. 2000). When publishing the currently most established rating scale for NIA, Barnes (1989) discussed testing its validity by using an electronic movement meter to objectively quantify the restless activity of patients.

Previous accelerometric findings (Gardos et al. 1992, Poyurovsky et al. 2000) of diurnal activity in NIA are difficult to interpret because not all the motor activity can be accounted for akathisia and even hospitalized patients can have very different daily routines and activities. Quantification of motor activity and qualitative analysis of movement patterns should occur in a standardized setting, which is still as naturalistic as possible to allow spontaneous, individual motor activity of subjects to take place.

As the term "akathisia" suggests, the inability to sit still is a pathognomonic and diagnostic feature of NIA (American Psychiatric Association 1994, 2000), leading to the hypothesis that rest-activity during sitting would be abnormal, both quantitatively and qualitatively, in NIA.

The specific purpose of this study was to develop actometric diagnostics and monitoring of akathisia and to find an objective diagnostic marker and indicator of symptom severity in NIA.

4.2. RLS study

The severity of symptoms in RLS has also been difficult to quantify. Due to the lack of physiological markers, non-validated rating scales have been used to measure symptom severity (Chokroverty and Jankovic 1999). Both subjective and objective assessment methods, including actometry, should be further developed to provide more reliable evidence of therapeutic impact (Hening et al. 1999a). The most commonly used objective diagnostic sign and measure of symptom severity, the PLM index, is unspecific and non-sensitive for RLS (Montplaisir et al. 1997, 1998, 1999). Moreover, it is not strictly a quantitative measure, as it requires the visual identification of typical movement patterns. EMG recording of quantitative motor activity in a standardized setting requiring immobilization of the subject (Montplaisir et al. 1998) has the disadvantage of a non-naturalistic laboratory method, not allowing natural, spontaneous movement of subjects.

As the diagnostic criteria of RLS (IRLSSG 1995) include a desire to move, uncomfortable sensations and motor restlessness, but not necessarily PLM, voluntary motor restlessness in response to subjective symptoms is an essential feature of RLS. Because the symptoms are elicited or worsened by rest, natural motor activity during rest is hypothesized to be a central marker of symptom severity.

The purpose was to develop actometric diagnostics and monitoring of RLS by finding an objective diagnostic marker and indicator of symptom severity in RLS. Another purpose was to clarify differential diagnostics of motor symptoms between RLS and NIA.

4.3. ASP/ADHD study

As hyperactivity is the most discriminative feature of ADHD (Halperin et al. 1992) and is most prominent in structured situations requiring inhibited activity (Teicher 1995, Dane et al. 2000), a quantitative assessment of hyperactivity in a standardized setting is expected to be a useful measure of symptom severity. Since some of the ADHD symptoms may persist until adulthood (Gittelman et al. 1985, Mannuzza et al. 1993) and are linked to antisocial development (McCracken et al. 2000), the objective evaluation of motor hyperactivity in an adult sample of ASP patients with ADHD is of interest. Hyperactivity may be more persistent than other symptoms of ADHD in adulthood (Teicher et al. 1995).

The quantification of rest-activity and qualitative analysis of movement patterns during rest in ASP with ADHD was hypothesized to yield abnormal findings and to offer a possibility of comparison with NIA, which may serve as a model of hypodopaminergic hyperactivity disorder. The central hypodopaminergic pathophysiological model of ADHD elicits the hypothesis of similarities between NIA and ADHD hyperactivity.

The purpose was to assess residual hyperactivity symptoms in adult ADHD in a violent, antisocial population and to compare the actometric findings between ADHD and NIA.

4.4. Asperger study

Because movement disorders, motor hyperactivity and hypoactivity are reported in autism (Gillberg 1995, Gillberg and Billstedt 2000, Ringman and Jankovic 2000, Smith 2000, Weimer et al. 2001), an objective quantification of rest-activity and qualitative analysis of movement patterns with actometry would be useful for clinical and scientific neuropsychiatric assessment. The abnormal level of motor activity described in autism has never been objectively quantified before. The motor disturbance related to autism seems to be especially prominent in Asperger's disorder (Iwanaga et al. 2000).

The overlapping features with schizophrenia spectrum disorders (Gillberg 1998b), motor features in common with Parkinson's disease (Vilensky et al. 1981), vulnerability to neuroleptic-induced EP symptoms (Campbell et al. 1997) and hypodopaminergic findings in autism (Ernst et al. 1997) suggest the possibility of idiopathic EP movement disorders, such as akathisia in Asperger's disorder, which were anticipated to show up in actometric recording of rest-activity. The rest-activity of Asperger patients was hypothesized to be abnormal.

The purpose was to quantify motor activity at rest and to find possible abnormal movement patterns.

5. SUBJECTS

5.1. Ethical considerations

An informed consent was used in each of these studies, and they were all approved by the Ethics Committee of Helsinki University Central Hospital (HUCH). Ambulatory monitoring by actometry is a non-invasive method that does not cause any pain for the subjects.

5.2. NIA study

Ten NIA patients were recruited from hospitalized psychiatric patients at HUCH either referred to treatment for psychotic disorder or referred to the NIA study. The clinicians in charge of the treatment made the initial diagnosis of NIA and excluded psychotic agitation before allowing the patients to enter the study. Inclusion criteria were a diagnosis of acute NIA as defined by DSM-IV (American Psychiatric Association 1994), sufficient co-operativeness for the study procedures and an age between 18 and 65 years. Exclusion criteria were acute abstinence syndromes and recent substance abuse, clinically relevant somatic or neurological disorders, and clinically observable neuroleptic-induced parkinsonian symptoms to exclude the possible interfering effect of tremor or hypokinesia on motor activity. Laboratory abnormalities were exluded by a test battery including blood cell count, blood

glucose, serum transaminases, glutamyl-transferase, creatinine and thryroid-stimulating hormone.

An age- (+/- 5 years) and sex-matched healthy control was selected for each patient among hospital employees. Exclusion criteria for the healthy controls were the same as for the NIA patients, in addition to current use of any medication, and any self-reported psychiatric disorders. The mean age of the NIA patients was 34.5 years and 35.3 of the controls. Subjects comprised five female and five male patients with schizophrenia spectrum psychotic disorder. Seven patients were on conventional neuroleptics, two patients were taking risperidone together with a sedative, low-potency neuroleptic, and one used sulpiride. All the NIA patients were able to maintain a sitting position for the recording time (30 min) despite an akathisia-related urge to move.

5.3. RLS study

Study subjects comprised 15 patients with idiopathic RLS, recruited by a monthly health magazine and a control group of 15 healthy hospital employees.

Inclusion criteria for the RLS patients was an age of 18-65 years and a diagnosis of RLS (IRLSSG 1995) together with chronic (>1 year), frequent (>50% of nights) and subjectively distressing or harmful symptoms. Exclusion criteria were current medication or medication during the past two weeks, a history of regular or long-term use of hypnotics, sedatives, dopaminergic- or other psychoactive drugs, major somatic illnesses or traumas, secondary causes of RLS, any medical causes of insomnia other than RLS, any clinical sleep disorders other than RLS, and any past or present psychiatric axis 1 disorders uncovered during a structured clinical interview for diagnosis (SCID) (First et al. 1997a). Axis 2 disorders were also controlled for by SCID (First et al. 1997b), although they were not an exclusion criterion. Clinical somatic and standardized neurological examinations with laboratory tests (blood cell count, serum ferritin, serum glucose, serum creatinine and serum glutamyl-transferase) were performed.

Healthy controls aged between 18 and 65 years were included. Exclusion criteria were the same as listed above, except that psychiatric exclusion was based on their own report instead of SCID, and the clinical somatic assessment included only the laboratory tests and taking of medical history if no reason for further examination emerged. Furthermore, any reported RLS symptoms were exclusion criteria for the control group.

The mean age in the RLS group was 50.3 years (SD 11.2, range 26-62) and in the control group 49.3 years (SD 6.46, range 33-57), the difference between the groups being non-significant (t=0.300, p=0.767). Male to female ratio was 1:14 in both groups. No significant differences were present in the haemoglobin (t=0.109, p=0.914) and serum ferritin levels (t=1.19, p=0.246) between the RLS (mean haemoglobin 138, SD 12.0, mean serum ferritin 60, SD 54.7) and the control (mean haemoglobin 138, SD 11.5, mean serum ferritin 41, SD 30.1) groups.

5.4. ASP/ADHD study

Fifteen ASP patients with ADHD and 10 NIA patients were recruited from the Department of Psychiatry of HUCH and the Hesperia Psychiatric Hospital. The control sample consisted of 15 employees or medical students of HUCH.

The ASP/ADHD sample comprised consecutive cases of violent offenders in court-ordered mental examination by the Forensic Psychiatric Department of HUCH. Subjects with a diagnosis of ASP according to diagnostic interview (First et al. 1997b) and aged between 18 and 65 were included. All of the subjects of this sample had a history of ADHD symptoms based on subjective reports, reports of other informants and childhood records. The symptoms retrospectively fulfilled the diagnostic criteria for ADHD in DSM-IV (American Psychiatric Association 2000). Most of them displayed persistent residual symptoms of childhood ADHD. Current restless psychiatric conditions (mania, agitated depression, generalized anxiety) were excluded by SCID (First et al. 1997a). Exclusion criteria were current medication, physical illness or substance abuse during the last two months. Abstinence was controlled by urine screening. A history of neurological disorder other than ADHD was also an exclusion criterion.

Laboratory abnormalities were excluded in both the ASP/ADHD group and NIA group by a test battery including blood cell count, blood glucose, serum transaminases, glutamyl-transferase, creatinine and thryroid-stimulating hormone.

The NIA sample, which consisted of neuroleptic-treated in-patients recovering from psychosis, was recruited by their clinicians who made the initial diagnosis of NIA and excluded those with psychotic agitation. Inclusion criteria were diagnosis of NIA confirmed by DSM-IV (American Psychiatric Association 1994, 2000) and ability to co-operate sufficiently for measuring controlled rest-activity. Thus, patients who were excessively psychotic or had such severe akathisia that they were unable to remain seated for 30 min were excluded. Patients with clinically relevant somatic diseases or neurological disorders other than NIA were also excluded.

Exclusion criteria for the healthy controls were current use of any medication and any self-reported clinically relevant somatic or psychiatric disorders.

All subjects were male. The mean age was 34.3 years (SD 9.9, range 19-49) in the ASP/ADHD group, 33.3 years (SD 12.7, range 20-55) in the NIA group, and 33.8 years (SD 12.7, range 23-56) in the control group.

5.5. Asperger study

Ten individuals with Asperger's Disorder, seven males and three females, aged 21-44 years (mean 29.8, SD 8.0), were recruited from the Helsinki Asperger Centre. Inclusion criteria were an age of 18-65 years and a diagnosis of Asperger's disorder according to DSM-IV (American Psychiatric Association 2000). Exclusion criteria were major somatic diseases, past or present psychosis, current substance abuse and current psychopharmacological treatment. All subjects were unmedicated except one, who had been on stabilized thyroxin substitution since childhood. The minimum wash-out period for benzodiazepine-like hypnotics and melatonin was two weeks, for antidepressive drugs three months and for neuroleptic drugs one year. None of the subjects had used hypnotics regularly, and none had had long-term neuroleptic exposure.

Somatic disorders were ruled out by clinical examination and laboratory tests, including electrocardiogram, serum glucose, sodium, potassium, phosphorus, calcium, creatinine, glutamyl-transferase, thyroxine, thyroid-stimulating hormone, prolactin, aminotransferases, C-reactive protein, ferritin, blood sediment, complete blood cell count and urine screen. Past or present psychosis was excluded by a structured diagnostic interview, SCID (First et al. 1997a), and other axis 1 and axis 2 disorders were controlled for (First et al. 1997b). No current affective pathology emerged in the patients except in one, who fulfilled the criteria of an episode of recurrent depression. The detected comorbidity with anxiety and personality pathology, which is common in these patients, may be explained by overlapping diagnostic features (American Psychiatric Association 2000, Gillberg and Billstedt 2000). It is under debate whether these overlapping disorders, including social phobia, OCD and schizoid personality, should be diagnosed with Asperger's disorder or not. A standard neurological examination and magnetic resonance imaging of the head were performed on all patients to exclude neurological pathology or disorders other than Asperger's. Their cognitive level was controlled by psychometric assessment.

An age- and sex-matched group of 10 healthy controls aged between 23 and 47 years (mean 30.8, SD 8.8) were recruited from hospital employees. Exclusion criteria for healthy controls were current use of any medication and any clinically relevant self-reported somatic or psychiatric disorders.

5.6. Overlap of samples

ASP/ADHD study subjects included five healthy controls and five NIA patients of suitable age and male sex from the NIA study.

Asperger study subjects included three healthy controls used in the NIA study and seven used in the ASP/ADHD study.

Altogether, the study material consisted of a combined group of 35 healthy controls (mean age 41.6 years, 19 females and 16 males), a combined group of 15 NIA patients (mean age 36.5 years, 5 females and 10 males), 15 RLS patients, 15 antisocial

ADHD patients, and 10 Asperger's disorder patients. Thus, the total number of study subjects was 90.

6. METHODS

6.1. Actometry

Ambulatory activity monitors of type PAM3 (IM-systems, Baltimore, USA) were used to record motor activity of subjects. The mode of data collection in PAM3 is based on digital integration (see sections 2.4.1. and 3.6.). These actometric monitors contain triaxial piezoelectric accelerometer sensors that react to acceleration rates above 0.1 g. The recorded acceleration signal is sampled as an activity count at a rate of 40 Hz, and the values for each sample are used to calculate the average activity counts within a chosen time window, 0.1 s. The time window is sufficiently small to allow analysis of movements within the range of EP movement disorders (see section 2.4.3.) With the 0.1 s time window, 1 g of acceleration equals approximately 106 activity counts. The movement index for a chosen time period is the sum of average activity counts for each time window included in this period.

Three-channel actometry was used instead of the more usual one-channel wrist actigraphy because the main focus of this study was lower limb activity. Two of the monitors were attached to lower limbs, one to each ankle, and one monitor was attached to the waist (just above the navel) to record the activity of the trunk and whole body. The third monitor on the waist allows the relationship between lower limb activity and activity of the trunk to be analysed. Besides it also served as a reference monitor to control for the time consistency of reported and measured gross movements and events during nocturnal recording to exclude time periods out of the bed. Actometers are small, computerized movement detectors, which do not influence the normal moving of the subject. Absolute movement indices were divided by 1000 to allow more convenient handling of the figures. Absolute movement indices are reported for controlled rest, because it is a fixed time period of 30 min, but relative movement indices are reported for nocturnal recording as the time-in-bed

varies individually among the subjects. Thus, the nocturnal motor activity is the absolute movement index for the time-in-bed divided by the minutes spent in bed.

6.2. Controlled rest-activity

Thirty minutes seems to be the maximum time that akathisia patients are able to maintain the sitting position (Rapoport et al. 1994) and is long enough for motor symptoms to become manifested (Barnes 1989). Moreover, it is a usual length of a clinical interview while simultaneously keeping the patient's attention focused on the discussion. The patient is not instructed to sit still during the interview to allow spontaneous, natural movements. However, it is customary for a co-operative patient to remain seated in a medical interview even in the presence of an urge to stand up and walk. Because rest-activity during sitting was the measure of comparison, those NIA patients who were unable to maintain the sitting position for 30 min were excluded from the study (see sections 5.2. and 5.4.). Most often, patients who are able and willing to give informed consent are also sufficiently co-operative to follow this type of study procedure.

Controlled rest-activity is recorded in a standardized setting, in which the subject is observed to confirm that the sitting position is maintaned. The standardized setting is a 30-min clinical interview in a clinical assessment room. The solid, standard chair of the subject is provided with a support for the back and hands and is located two metres from the interviewer, the clinician. The conversation with the study subject is characterized by a low-stress, neutral atmosphere created by open questions and adhering to the themes voluntarily discussed by the subject. The interview opens with questions about the overall health record including somatic, neurological and psychiatric history of symptoms, possible treatments, previous examinations and routine health check-ups. Next, questions about the activity rhythms of the subject are posed concerning daily activity, sleeping and physical training habits. Independent of the study group, each subject is asked about possible movement disorder or hyperactivity symptoms. The subject is also encouraged to talk about eating, drinking and smoking habits. Naturally, the subjects are aware of the actometric recording and

the monitors attached to their bodies, but the idea of the interview is to focus their attention away from the monitors and from their own movements to allow as naturalistic a setting as possible while maintaining a standardized and controlled situation.

Controlled rest-activity of lower limbs (the average of right and left ankle activity) is the main outcome parameter. In the NIA study, only activity of the non-dominant ankle (left ankle) was first used for statistical comparison (Study I), because no significant differences in laterality were found. The non-dominant side is typically chosen for actometric recording (Nagels et al. 1996). Purposeful movements, which can mask the more pathological movement patterns, are lateralized to the dominant side by definition (Springer and Deutch 1993). In actometry, both qualitative and a small quantitative difference are present between the dominant and non-dominant upper limb activities (Nagels et al. 1996). However, losing data in unilateral analysis of motor activity may occurr, and defining motor dominance is sometimes uncertain. For these reasons, and to compare the results with the three following studies, the inter-group comparisons in the NIA study were re-analysed here with the data obtained from both lower limbs.

The ankle-waist ratio of controlled rest-activity is a secondary outcome parameter. It reflects the distribution of motor activity between the trunk and lower limbs. Therefore, a relatively high ankle-waist ratio indicates that the emphasis of body activity is on the lower limbs. A high lower limb activity combined to a high ankle-waist ratio thus indicates motor hyperactivity specific to the lower limbs.

The most consistent recording sessions (30 min within a 2-hour period) were in the NIA and RLS studies, which represented the earliest (9 am-11 am in the former) and the latest (5 pm-7 pm in the latter) recording times. The subjects in the other two studies were recorded within these time frames, mostly in the afternoon.

6.3. Day-time activity

Motor activity was measured in all the subjects of the NIA study between 9 am and 11:30 pm, and the period of controlled rest was included in the day-time recording

between 9 am and 11 am. Quantification of daily motor activity was performed with the same three-channel recording (see section 7.1.), which was also used in quantification of controlled rest-activity in all patient groups and of nocturnal activity in the RLS group.

6.4. Nocturnal activity

The circadian rhythm and the qualities of a sleep disorder in RLS implicated an assessment of nocturnal activity in addition to controlled rest-activity. The nocturnal activity was recorded in all subjects during the night following the recording of controlled rest-activity.

Nocturnal activity is measured by a home-recording to obtain a naturalistic assessment. The subjects carried the ambulatory monitors with them at home, and the motor activity during time-in-bed was analysed. Subjective reports of time spent in bed were used to calculate the nocturnal activity during time-in-bed. Time-in-bed was defined as the period between going to bed to sleep and getting up in the morning. The time consistency of the reported periods out of bed during night-time was controlled for by a three-channel recording (see section 7.1.).

The nocturnal recording was divided into the reported period of sleep latency and sleep-time in order to analyse motor activity during sleep latency and sleep, although subjectively reported time of sleep latency can not be considered an accurate and reliable measure (Spinweber et al. 1985). Thus, the main parameter was nocturnal activity during time-in-bed, including periods of both sleep and wakefulness. Because no validated symptom-severity scale was available, we chose the reported length of sleep latency to represent a non-actometric, indirect variable of symptom-severity or symptom-distress level to search for inter-correlations with the actometric data.

6.5. PLM index

Nocturnal PLM index for time-in-bed was defined by nocturnal actometric recording including both periods of sleep and wakefulness. Both PLM during sleep and while awake has been used as a measure of symptom severity in RLS (Allen and Earley

2001), and actometric quantification of PLM during time-in-bed, including both wakefulness and sleep, has been developed to measure symptom severity (Kazenwadel et al. 1995).

The recommended screening criteria for PLM (Atlas Task Force of the American Sleep Disorders Association 1993), later applied to actometry (Kazenwadel et al. 1995, Collado-Seidel et al. 1999), were used by an experienced blind rater to obtain quantitative data by calculating the PLM index. The criteria for actometric scoring of PLM included a duration of leg movements between 0.5 and 5 s, an inter-event interval between 4 and 90 s and occurrence of at least four consecutive movements fulfilling the above criteria. PLM index is the amount of PLM per hour of time-in-bed (Kazenwadel et al. 1995). The discriminating qualities of the PLM index and the general motor activity for time-in-bed were compared.

6.6. Assessment scales

The Barnes Akathisia Rating Scale (BARS) (Barnes 1989) was used for assessment of clinical akathisia symptoms in all subjects. The symptom severity of RLS was assessed by the Visual Analogue Scale (VAS), as no validated rating scales were yet available. A retrospective evaluation of childhood ADHD symptoms was obtained from Asperger patients using the Wender Utah Rating Scale (WURS), which has been validated as a diagnostic aid to evaluate the presence and severity of childhood symptoms of ADHD in adult patients (Ward et al. 1993).

6.7. Haematological and biochemical assessment

Basic laboratory assessment was performed on all patient groups and on the control group of RLS patients to exclude somatic disorders. Test batteries used were slightly different in each study sample (see sections 5.2.-5.5.).

Assessment of serum ferritin is essential in RLS since iron deficiency is a risk factor for RLS and iron status is correlated with symptom severity (Aul et al. 1998, Sun et al. 1998).

6.8. Other procedures

In the RLS study, all subjects filled in sleep diaries during the nocturnal actometric recording.

In the NIA study, five of the patients were switched to an atypical antipsychotic (olanzapine) during the study, and the actometric recording was performed again two weeks after the medication change. As switching antipsychotic medication from a conventional to an atypical drug is a primary treatment option in NIA, a remission of NIA symptoms was expected. This offered the possibility to monitor the treatment response with both clinical evaluation (by BARS) and actometry. Furthermore, a comparison between symptomatic NIA and NIA in remission was performed as well as a comparison between NIA in remission and healthy controls. The medication change was based on clinical judgement.

6.9. Statistical analysis

Because actometric data were non-normally distributed, non-parametric statistical tests were used in data analysis. The statistical significance of intercorrelations in the data was analysed with Spearman's test. In Studies II-IV, the inter-group comparisons were performed using the Mann Whitney U-test (U reported as a test value), and in Study III the inter-group comparison between all three groups was performed with the Kruskal-Wallis test (Chi-square reported as a test value).

Study I, focusing on NIA, was originally analysed with a parametric t-test because data were assumed to be normally distributed. Later, the statistical significance of results was confirmed with the non-parametric Wilcoxon test for paired samples (Z reported as a test value), used in this dissertation, which is more suited for the non-normally distributed, paired parameters of this study.

Table 3

Average actometric values of 10 patients with neuroleptic induced akathisia (NIA) and 10 healthy controls. Statistical comparison between the groups.

	NIA			Controls			Comparison	
	Med	Q1 - Q3	Range	Med	Q1 - Q3	Range	Z	p
MOVEMENT INDICES:								
Left ankle activity	80	55-93	29-130	0.59	0.051-2.4	0.003-4.1	-2.803	0.005
Right ankle activity	77	65-130	23-230	1.1	0.54-4.1	0.0-4.6	-2.803	0.005
Lower limb activity[1]	81	60-110	26-160	0.95	0.35-3.5	0.0015-4.0	-2.803	0.005
Ankle-waist ratio[2]	2.8	2.0-3.7	1.4-4.2	0.33	0.11-0.99	0.0-2.2	-2.803	0.005

Average actometric values and BARS scores of **5** NIA patients before (symptomatic), and after the medication change (in remission).
BARS = Barnes Akathisia Rating Scale

	NIA (symptomatic)		NIA (in remission)		Comparison	
	Med	Range	Med	Range	Z	p
MOVEMENT INDICES:						
Lower limb activity[1]	89	26-130	1.1	0.38-24	-2.023	0.043
BARS	2	2-4	0	0-1	-2.032	0.042

Statistics:
Med = median, Q1-Q3 = interquartile range
p = values for statistical difference between groups
Z = test values for Wilcoxon paired sample test

Movement index derivatives:
1. Mean value of right and left ankle movement indices
2. Movement index of the waist divided by the lower limb activity index

7. RESULTS

For results, see Tables 3-7 and Figs 1-2.

7.1. NIA study

Lower limb controlled rest-activity was significantly higher in NIA patients than in healthy controls, and it discriminated the two groups with no overlap (Table 3). The

ankle-waist ratio during controlled rest also significantly differentiated the NIA patients from controls (Table 3), but no significant differences were found in either lower limb activity or the ankle-waist ratio when comparing daily motor activity between NIA patients and healthy controls.

When the five NIA patients whose medication was changed immediately after the first recording were compared to themselves after two weeks, in remission phase, the decrease of their lower limb activity was significant (Table 3). Moreover, their median lower limb activity was at the level of their healthy counterparts, or even lower, showing no significant difference compared with controls (Table 7).
Qualitatively, akathisia appeared in lower limb actometry as periodic, rhythmic 0.7-1.6 Hz activity episodes increasing towards the end of the 30 min of controlled rest.

The median BARS global item score of the patients was 2.5 (between 2, mild, and 3, moderate akathisia). Their scores ranged from 2 to 4 (marked akathisia). For those five patients whose medication was changed, the initial scores decreased significantly in remission (Table 3). The BARS scores seemed to be positively and linearly correlated with controlled rest-activity, but probably due to the small sample size, the correlation did not reach statistical significance ($r=0.536$, $p=0.110$).

7.2. RLS study

The higher controlled rest-activity differentiated the RLS patients from healthy controls significantly. The difference remained significant when analysing both lower

Table 4

Average actometric values of 15 patients with restless legs syndrome (RLS) and 15 healthy controls. Statistical comparison between the groups.

	RLS			Controls			Comparison	
	Med	Q1 - Q3	Range	Med	Q1 - Q3	Range	U	p
CONTROLLED REST ACTIVITY:								
Left ankle activity	12	8.4-14	3.5-47	0.9	0.48-2.5	0.15-4.8	2.0	0.000
Right ankle activity	12	8.9-18	1.8-30.0	0.9	0.40-1.8	0.12-4.4	8.0	0.000
Lower limb activity[1]	11	8.4-20.3	2.8-30.0	1.1	0.43-2.8	0.21-.3.5	4.0	0.000
Ankle-waist ratio[2]	1.3	0.62-2.2	0.41-6.1	0.60	0.37-1.6	0.29-6.8	70.0	0.078
NOCTURNAL ACTIVITY:								
Left ankle activity	720	340-910	140-2000	48	32-150	15-290	7.0	0.000
Right ankle activity	650	380-890	160-1300	80.4	23-180	12-280	5.0	0.000
Lower limb activity[1]	650	520-860	260-1500	58	27-140	13-220	0.00	0.000
PLM INDEX:	1.4	0.00-7.4	0.0-46	0.00	0.00-0.00	0.00-1.5	47	0.002

Statistics:
Med = median, Q1-Q3 = interquartile range
p = values for statistical difference between RLS and control groups
U = test value for Mann-Whitney U-test

Movement index derivatives:
1. Mean value of right and left ankle movement indices
2. Movement index of the waist divided by the lower limb activity index

PLM index: periodic limb movement index

limbs separately (Table 4). The median ankle-waist ratio was higher in the RLS group than in controls, but the difference did not reach statistical significance (Table 4). There was some overlap between the controlled rest activity of the RLS patients and the healthy controls (Table 4). The best discriminative sensitivity was 93% and specificity was 100% with a threshold value of 5.00.

The nocturnal lower limb activity per minute was significantly higher in the RLS group compared with controls and the difference was significant for both lower limbs analysed separately (Table 4). The small laterality differences were non-significant in both the RLS group ($Z=-0.227$, $p=0.820$) and the control group ($Z=-0.341$, $p=0.733$). The nocturnal rest-activity discriminated the RLS patients from healthy controls with a sensitivity of 100% and a specificity of 100% when using a threshold value of 250. The nocturnal activity was significantly correlated ($r=0.744$, $p<0.0005$) with the controlled rest-activity.

The median of the reported sleeping time was 388 min in the RLS group and 377 min in the control group, showing no significant difference between the groups ($U=111.5$, $p=0.967$). The sleep latency was significantly longer ($U=62.5$, $p=0.036$) in the RLS group (median 30 min) than in the control group (median 24 min). The length of sleep latency was positively and significantly ($p=0.035$, $r=0.386$) correlated with nocturnal activity. There was a trend towards a positive inter-correlation between sleep latency and controlled rest-activity, but it was non-significant ($r=0.289$, $p=0.122$). Motor activity during sleep-latency differentiated the RLS group from the controls significantly ($U=4.0$, $p<0.0005$), as did the activity during sleep ($U<0.0005$, $p<0.0005$).

Healthy controls (n=6) with a sleep latency of 30 min or more (median 40, range 30-90) were compared with RLS patients (n=9) within the same range (median 30). The nocturnal activity was again significantly ($U<0.0005$, $p=0.001$) higher in the RLS patients (median 715) than in the healthy controls (median 99.0) in subgroup analysis, and nocturnal activity still discriminated RLS patients (range 313-1510) from healthy controls (range 26.6-221) with no overlap. The controlled rest-activity was also significantly ($U=2.0$, $p=0.002$) higher in the RLS patients (median 9.66) than in healthy controls (median 0.863) within this subgroup.

The nocturnal PLM index differentiated the RLS patients from healthy controls significantly (table 4). The best discriminative power was obtained with the threshold value 0.5: sensitivity 67% and specificity 87%. The range of the healthy controls was totally overlapped by the range of the RLS group (table 4). The PLM index was positively and significantly correlated to nocturnal activity ($r=0.520$, $p=0.003$) and to controlled rest-activity ($r=0.621$, $p<0.0005$). There was also a positive, but non-significant ($r=0.341$, $p=0.065$) correlation to the length of sleep latency.

In qualitative analysis the typical PLM pattern fulfilling the screening criteria (Kazenwadel et al. 1995) was detected in 10 RLS patients and in 2 healthy controls during night-time and in 5 RLS patients and in none of the healthy controls during the controlled rest. Other type of unspecific motor activity was more predominant in both groups. Furthermore, a motor pattern resembling to PLM, but not fulfilling the screening criteria, was quite common in RLS during nocturnal recording. The duration of these movements were often longer than allowed by PLM criteria, probably caused by clustering of shorter movements into longer movement complexes. The considerable amount of random background activity may also have complicated the diagnosis of PLM patterns.

During the 30 minutes of the controlled rest, the RLS group typically showed many random, transient, short activity intrusions of 1-10s related to changing of the pose and moving the legs. This was sometimes intermixed with a more continuous, fluctuating activity of irregular or changing rhythm and amplitude obviously corresponding to the motor restlessness due to uncomfortable sensations during rest. Just a few short, random small-amplitude activity peaks were detected in the healthy controls except in one subject, who showed a 30s period of continuous activity on the right channel while she was circling and stretching her right ankle.

In clinical assessment, 8 of the RLS patients scored 2 in BARS due to their subjective feelings of restlessness localized to legs and an urge to move while seated. Other 7 patients and all the healthy controls scored zero. The serum-ferritine was not correlated to any of the study parameters.

7.3. ASP/ADHD study

Median lower limb rest-activity of the ASP/ADHD group was significantly higher than the activity of the controls (Table 5). As expected, the lower-limb activity of NIA patients was also significantly higher than the activity of control subjects (Table 5). Lower limb activity of the ASP/ADHD group fell between that of the control and the NIA groups. The activity range of the ASP/ADHD group was clearly discriminative of the control range, but some overlap occurred with the range of the NIA group (Table 5).

Ankle-waist ratio, reflecting the emphasis of motor activity on the lower limbs, differentiated ASP/ADHD patients significantly from controls, and as in previous findings, the ankle-waist ratio also significantly differentiated NIA patients from controls (Table 5).

When comparing the ASP/ADHD group to the NIA group, the lower limb activity of the former was significantly lower ($U=26.0$, $p=0.004$). The ankle-waist ratio showed no significant difference between groups ($U=46.0$, $p=0.115$), although a trend was found for higher ankle-waist ratios in NIA patients than in ASP/ADHD patients, reflecting more disturbed movement distribution in NIA patients. When comparing all three groups, a significant group effect was present in both lower limb rest activity and ankle-waist ratio (Table 5).

The three ASP/ADHD patients diagnosed with current affective or anxiety disorders were compared with the other 12 ASP/ADHD patients: their lower limb activity did not differ significantly ($U=13.0$, $p=0.470$) from that of the others, nor did the ankle-waist ratio show any significant difference. When excluding the three cases with affective/anxiety disorders from the comparison of the ASP/ADHD sample to the control group, all significant differences between the groups remained unchanged.

Qualitative analysis of the actometric raw data revealed similarities between the ASP/ADHD and the NIA samples: 13 out of 15 patients in the ASP/ADHD sample demonstrated regular rhythmic activity periods of 0.85-1.80 Hz (mean 1.2 Hz, SD 0.3), which were indistinguishable from the earlier-mentioned akathisia pattern. The

Table 5

Average actometric values of 15 antisocial personality disorder patients with attention deficit hyperactivity disorder (ASP/ADHD), 10 patients with neuroleptic-induced akathisia (NIA) and 15 healthy controls (CON). Statistical comparison of the two patient groups with controls, and comparison of the three groups.

	ASP/ ADHD				ASP/ADHD vs. CON	NIA				NIA vs. CON	CON				ASP/ADHD vs. .NIA vs. CON
	Med	Q1 - Q3	Range	U	p 1	Med	Q1 - Q3)	Range	U	p 1	Med	Q1 - Q3	Range	Chi square	p 2
MOVEMENT INDICES:															
Left ankle activity	21.5	15.5-35.9	9.1-80.3	0.000	0.000	55.3	33.4 -94.6	23-129	0.000	0.000	0.84	0.14-1.68	0.06-3.3	30.0	0.000
Right ankle activity	15.5	10.6-44.2	6.6-62.7	0.000	0.000	59.0	24.5 -82.7	16-228	0.000	0.000	0.76	0.04-2.72	0.0-.4.5	31.0	0.000
Lower limb activity [1]	19.9	14.0-36.3	13-66	0.000	0.000	57.1	43.5-83.1	20-160	0.000	0.000	0.92	0.07-1.85	0.0015-4.0	30.4	0.000
Ankle-waist ratio[2]	2.01	1.00-4.15	0.23-6.7	23.0	0.000	2.73	2.22-5.20	1.4-7.4	0.000	0.000	0.55	0.16-0.79	0.02-1.0	22.9	0.000

Statistics:
Med = median, Q1-Q3 = interquartile range
p1 = values for statistical difference between ASP and CON as well as between NIA and CON: Mann-Whitney U-test (two-tailed).
P2 = values for statistical difference between the three groups: ASP, NIA and CON: Kruskal-Wallis test.
U = test value for Mann-Whitney U-test
Chi square = test value for Kruskal-Wallis test

Movement index derivatives:
1. Mean value of right and left ankle movement indices
2. Movement index of the waist divided by the lower limb activity index

frequency range of rhythmic activity in the NIA sample here (range 0.65-1.7 Hz, mean 1.1 Hz, SD 0.33) was almost identical. The healthy controls demonstrated no such pattern. ASP/ADHD had more movement episodes at the end of the controlled rest period, similar to akathisia patients. Unlike akathisia patients, however, the ASP/ADHD patients showed a considerable proportion of irregular motor hyperactivity among the akathisia-like patterns during controlled rest.

Clinically, no qualitative difference in the restless movements between ASP/ADHD and NIA groups was observed. Both groups demonstrated episodic, small-amplitude, jerky foot movements, consisting of heel tapping on the floor and foot shaking when the legs were crossed. The restless movements increased towards the end of the 30 min of sitting (controlled rest period) and were limited to the lower limbs. The subjects seemed to be unaware of their repetitive, monotonic movements. All subjects remained seated during the 30-min controlled rest period despite an urge to move reported by all NIA patients and the majority of ASP/ADHD patients.

The median BARS score in the ASP/ADHD group was 2 (range 0-3). Nine of the ASP/ADHD patients scored 2 (mild akathisia) or more in BARS and would have fulfilled the DSM-IV criteria of NIA except for neuroleptic exposure. Three ASP/ADHD patients scored 1 in BARS (questionable akathisia) and another three scored 0, showing no signs of akathisia in clinical evaluation. However, two of the latter demonstrated increased lower limb activity and a rhythmic akathisia-like pattern in actometry. In the NIA group, the median BARS score was 3 (range 2-4), and all healthy controls scored 0 in BARS. The increase of BARS scores in the ASP/ADHD group compared with the zero level in the control group was significant ($U=22.5$, $p=0.000$), but the BARS scores of the ASP/ADHD group were significantly ($U=23.5$, $p=0.002$) lower than those of the NIA group.

7.4. Asperger study

The controlled rest-activity of the lower limbs was significantly higher in the Asperger group than in their controls. The significant difference between the groups remained when both lower limbs were analysed separately (Table 6). No significant

Table 6

Average actometric values of 10 patients with Asperger's disorder and 10 healthy controls. Statistical comparison between the groups.

	Asperger			Controls			Comparison	
	Med	Q1 - Q3	Range	Med	Q1 - Q3	Range	U	p
MOVEMENT INDICES:								
Left ankle activity	11	7.4-19	0.79-38	0.38	0.094-1.2	0.026-4.1	3.0	0.000
Right ankle activity	7.6	2.7-23	0.38-37	0.85	0.011-1.3	0.00-3.3	10.0	0.002
Lower limb activity [1]	12	5.1-23	0.59-30	0.74	0.07-1.1	0.032-4.0	6.0	0.001
Ankle-waist ratio[2]	2.6	2.4-4.2	1.0-15	0.4	0.2-0.8	0.02-2.2	2.0	0.000

Statistics:
Med = median, Q1-Q3 = interquartile range
p = values for statistical difference between the groups
U = test value for Mann-Whitney U-test

Movement index derivatives:
1. Mean value of right and left ankle movement indices
2. Movement index of the waist divided by the lower limb activity index

laterality differences were found. The ankle-waist ratio was significantly higher in the Asperger group than in their controls (Table 6).

Eight of the 10 Asperger's disorder subjects demonstrated lower limb activity (range 5.5-30.4) above the range of the healthy controls (range 0.03-4.0), whereas the remaining two were within the range (Fig. 1). These eight also differed from the healthy controls in the qualitative analysis; they demonstrated a regular, rhythmic movement pattern of frequencies between 0.5 and 1.0 Hz, which was not detected in the controls. The rhythmic motor activity of the Asperger's disorder subjects occurred in periods of 5-90 s. Those two Asperger's disorder subjects with low movement indices showed random, unspecific motor activity similar to the healthy controls. The rhythmic movement periods detected in the Asperger's disorder group occurred mostly towards the end of the 30 min of controlled rest.

Three of the 10 Asperger's disorder subjects demonstrated clinical akathisia symptoms, scoring 2 (mild akathisia) in BARS. Another three scored 1 (questionable akathisia) and the remaining four scored 0 (no akathisia). The lower limb movement indices for the whole Asperger's disorder group were not significantly correlated with BARS scores, but the correlation did reach a significant level ($r=0.76$, $p=0.03$) for those eight patients whose movement indices were above the range for healthy controls. The median lower limb activity was 24.3 for those who scored 2 in BARS, while for those scoring 1 or 0, it was 6.56. The difference between those with clinical akathisia symptoms (BARS 2) and those without (BARS 0-1) was significant ($U=0.0$, $p=0.017$). The average increase of BARS scores for the whole patient group was significant ($U=20.0$, $p=0.005$), when compared with the zero level of the control group.

Four of the 10 Asperger's disorder subjects scored above 46, the cut-off point in WURS, suggesting a history of ADHD. Their median lower limb movement index was 10.3, whereas for the six subjects below the WURS cut-off point, it was 13.4. No significant difference ($U=11.0$, $p=0.83$) was present between subgroups. The WURS scores had no correlation with any of the movement indices, nor were the WURS and the BARS scores inter-correlated. One of the Asperger's disorder subjects fulfilled the diagnostic criteria for RLS, but he reported having these symptoms infrequently, less

than once a month, and the symptoms were absent at the time of evaluation and actometric recording. This individual had the lowest movement indices, falling within the normal range.

In conclusion, high lower limb activity differentiated the Asperger's disorder group significantly from healthy controls, and the majority of Asperger's disorder patients also demonstrated a specific movement pattern, which was not detected in the controls.

7.5. Summary

Controlled rest-activity was significantly increased in all patient groups compared with healthy controls (Table 7), discriminating NIA and ASP/ADHD patients from healthy controls with no overlap (Fig. 1). The rest-activity of the NIA group was 85-fold compared with controls, and 84-fold compared with themselves in remission. The decrease in activity when NIA was adequately treated was significant. The NIA patients in the remission phase did not differ from healthy controls, showing an equal or even lower average activity level than their controls (Table 7).

The activity of the ASP/ADHD group was 22-fold compared with controls but was significantly lower than the activity of the NIA group (Table 7). The Asperger's disorder group showed a 16-fold increase of activity compared with controls, and the RLS group showed a 10-fold increase of activity. The increase of nocturnal activity in the RLS group was 11-fold compared with controls, and nocturnal activity, unlike controlled rest-activity, discriminated the RLS patients from controls with no overlap (Table 7).

When analysing the differences in controlled rest-activity, including all patient groups and all healthy controls, a significant group effect was present using the Kruskal-Wallis test (chi-square=72.02, $p<0.0005$). The highest activities were found in NIA patients, and next, in descending order, were the ASP/ADHD, Asperger's disorder, and RLS patients, while the lowest activity was measured, expectedly, in the healthy controls (Fig. 1).

Table 7: Summary of results.

CRA=controlled rest-activity; NIA=subjects with neuroleptic-induced akathisia; RLS=subjects with restless legs syndrome; ASP/ADHD=subjects with antisocial personality disorder and attention deficit hyperactivity disorder. For statistical test values, see section 6.9.

Study	Comparisons / Parameters	Patients	Patients	Controls	U/ Z/ Chi square	P
I	NIA vs. Controls	10	-	10		
	CRA (median)	80.6	-	0.95	-2.803	0.005
	NIA vs. NIA remission	5	5	-		
	CRA (median)	88.6	1.06	-	-2.023	0.043
	NIA-remission vs. Controls	5	-	5		
	CRA (median)	1.06	-	3.34	-1.214	0.225
II	RLS vs. Controls	15	-	15		
	CRA (median)	10.9	-	1.05	4.0	<0.0005
	Nocturnal Activity (median)	650	-	58.3	<0.0005	<0.0005
III	ASP/ADHD vs. Controls	15	-	15		
	CRA (median)	19.9	-	0.92	<0.0005	<0.0005
	ASP/ADHD vs. NIA	15	10	-		
	CRA (median)	19.9	57.1	-	26.0	0.007
	NIA vs. Controls	10	-	15		
	CRA (median)	57.1	-	0.92	<0.0005	<0.0005
	ASP/ADHD vs. NIA vs. Controls	15	10	15	30.4	<0.0005
IV	Asperger vs. Controls	10	-	10		
	CRA (median)	12.1	-	0.74	6.0	0.001

Qualitative differences were also found in the movement patterns between groups; NIA, ASP/ADHD and Asperger's disorder patients showed rhythmic, episodic activity increasing towards the end of the 30-min recording time. The frequency range of rhythmic activity was 0.5-1.8, and frequencies close to 1 Hz were the most prominent. This finding was clearest in the NIA group; in the other two patient groups, rhythmic, regular activity was intermixed with irregular and non-rhythmic activity. This type of activity was not detected in healthy controls or in RLS patients. Instead, the RLS group demonstrated a PLM pattern occurring at 5- to 90-s intervals, which is considered to be a pathognomonic feature of RLS (IRLSSG 1995, Kazenwadel et al. 1995).

Figure 1 (on the right)

A graphic illustration of quantitative motor activity during controlled rest (controlled rest-activity) of each study group. NIA=neuroleptic-induced akathisia; ASP/ADHD=antisocial personality disorder with attention deficit hyperactivity disorder; Asperger=Asperger's disorder; RLS=restless legs syndrome; Controls=healthy persons.

Figure 2 (page 76)

A graphic illustration of motor activity recorded during 30 min of controlled rest and movement patterns focused on the left ankle. A typical subject from each patient group (male, about 30 years) and two control subjects were selected.

The entire recording of controlled rest-activity, while the subject is sitting for 30 min is presented in the 1st column. The last 5 min of the controlled rest is presented in the 2nd column. A 10-s focus of the last 5 min, including movements, is presented in the 3rd column, except for control subjects, who displayed no movements during the last 5 min. For them, a 10-s focus of the highest activity throughout the recording is presented.

The focused time periods are indicated with spotted areas and arrows.

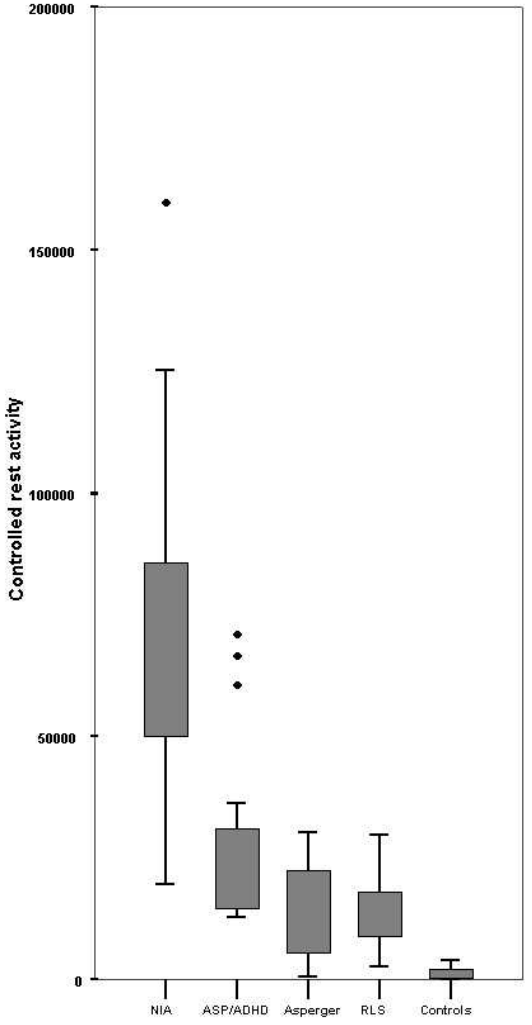
200000
150000
100000
50000
0
Controlled rest activity
NIA
ASP/ADHD
Asperger
RLS
Controls

Figure 1

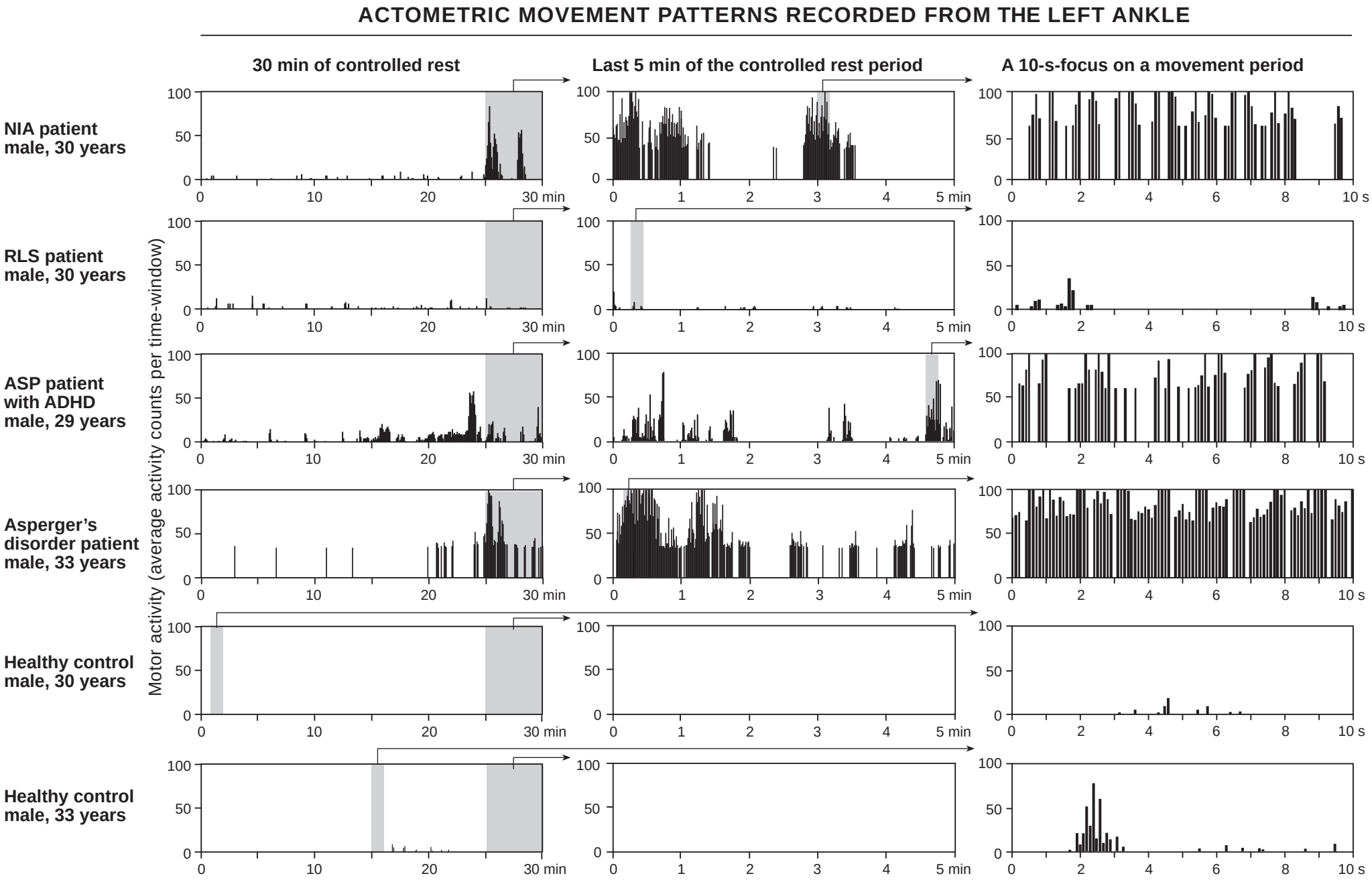
ACTOMETRIC MOVEMENT PATTERNS RECORDED FROM THE LEFT ANKLE
30 min of controlled rest
Last 5 min of the controlled rest period
A 10-s-focus on a movement period
NIA patient male, 30 years
RLS patient male, 30 years
ASP patient with ADHD male, 29 years
Asperger's disorder patient male, 33 years
Healthy control male, 30 years
Healthy control male, 33 years
Motor activity (average activity counts per time-window)
100
50
0
0 10 20 30 min
0 1 2 3 4 5 min
0 2 4 6 8 10 s

Figure 2

8. DISCUSSION

Motor activity during controlled rest was increased in each of the neuropsychiatric disorders studied here. Diagnosis had a significant effect on rest-activity. The highest increase in activity was observed in NIA patients, and the lowest in RLS patients. Controlled rest-activity discriminated both NIA and ASP/ADHD patients from healthy controls with no overlap. Each patient group also showed qualitative differences in motor activity compared with controls. NIA, ASP/ADHD and Asperger's disorder groups shared similarities in movement pattern, while RLS patients showed a distinctive pattern.

8.1. Motor characteristics of NIA

A marked increase of rest-activity and a pathognomonic movement pattern was seen in NIA patients when motor activity was measured in a standardized setting in which patients sat for 30 min. Akathisia, by original definition, means "not to sit", which is objectively demonstrated in actometry as an episodic, rhythmic motor restlessness increasing towards the end of the 30-min period. The predominant occurrence of movement episodes at the end of the rest period refers to an intensified urge to move during prolonged immobilization, or to a diminishing of the initial ability to suppress movements. These motor symptoms were accompanied by subjectively reported inner restlessness and an urge to move intensified by immobility. Contrary to controlled rest-activity, the daily motor activity level of NIA patients was not increased compared with healthy controls, which is possibly explained by the relative passiveness and limited activities of hospitalized patients. It seems that a greater amount of purposeful motor activity in work and leisure increases the day-time activity levels of healthy controls so that they are as active during the daytime as the NIA patients.

Although the results indicate that controlled rest-activity is clearly discriminative of NIA, the study setting can be criticized for using healthy persons as controls for hospitalized schizophrenic NIA patients instead of comparing schizophrenic in-patients with NIA with similar patients without NIA. This raises the question that could the increased rest-activity actually be due to schizophrenia instead of being a

consequence of NIA. However, the study of Gardos et al. (1992) shows that the baseline activity in schizophrenics is not higher than in healthy persons, in parallel with our findings. Thus, the high rest-activity of schizophrenic NIA patients in our study is likely mostly due to NIA rather than to schizophrenia. A standardized setting will typically elicit NIA symptoms and exclude the effect of purposeful daily activities on motor activity levels. The decrease of rest-activity to the level of healthy controls when NIA is treated further confirms that the increased rest-activity is really a phenomenon related to NIA. As the positive psychotic symptoms were already clinically stabilized at the inclusion phase, and the possible amelioration of negative symptoms would probably take longer than 2 weeks, the reduction of hyperactivity is unlikely to be explained by a marked change in psychotic symptoms.

The qualitative finding of an abnormal actometric movement pattern similar to the pattern previously described in NIA (Braude et al. 1984, Rapoport et al. 1994) also supports the value of controlled rest-activity as a diagnostic measure in NIA.

Actometry is probably more sensitive in detecting abnormal motor activity in NIA than the routine clinical assessment, especially in atypical forms of NIA with diagnostic problems such as hypokinetic akathisia (Tuisku et al. 2000). Hypokinetic akathisia is a form of subjective akathisia in which the clinical motor symptoms of akathisia are masked by the hypokinesia related to neuroleptic-induced parkinsonism. Van Putten and Marder (1986) used the term “subjective akathisia” for the first time to describe akathisia without observable restless movements. They postulated that mild akathisia may not be manifested as motor symptoms, particularly when a patient has a co-existing akinesia. The subjective component seems to be a fundamental and primary feature of akathisia (Van Putten 1975, Munetz 1983). Subjective akathisia poses a diagnostic challenge (Chung and Chiu 1996, Tuisku et al. 2000) because the DSM-IV criteria require objective motor restlessness (American Psychiatric Association 2000). Furthermore, the rating of subjective akathisia by BARS may be impossible (Tuisku et al. 2000). Despite its wide use among clinicians and the practicality and validity in classical akathisia, BARS disregards the richness of clinical features (Cunningham Owens 1999, Tuisku et al. 2000).

8.2. Differential diagnostics of NIA and RLS

Historically, because of the confusion between akathisia and RLS (Sachdev 1995a), the differential diagnostic features in actometry are of interest. In RLS, an increase in controlled rest-activity similar to NIA occurred, but it was more modest. In addition, some overlap was present between the range of healthy controls and that of RLS patients. RLS patients did not demonstrate the increased ankle-waist ratio typical of akathisia patients. Furthermore, the movement pattern in RLS was completely different from that in NIA, consisting of irregular, transient or fluctuating motor activity and sometimes PLM, in contrast to the clearly episodic, regular, rhythmic bursts of activity in NIA. The qualitative analysis of the movement pattern seems to be helpful for differential diagnosis between NIA and RLS. The PLM pattern recorded in the setting of controlled rest during wakefulness was not surprising because PLM are described to manifest not only in sleep but also during wakefulness in RLS (IRLSSG 1995). In fact, a restriction of the analysis to PLM occurring in sleep may result in an underestimation of the actual frequency of PLM (Kazenwadel et al. 1995).

8.3. Symptom severity of RLS

The nocturnal motor activity during time-in-bed differentiated RLS patients from healthy controls, showed good discriminative qualities and was better than the PLM index, which is a widely used measure of symptom severity and a diagnostic marker of RLS (Montplaisir et al. 1998, 1999). The specificity (67%) and sensitivity (87%) of the PLM index are close to those reported previously (68-81% and 73-81%, respectively) (Montplaisir et al. 1998). Nocturnal rest-activity proved to be the best actometric marker of RLS. The superiority of nocturnal activity over controlled rest-activity in discriminating RLS symptoms is probably due to the typical circadian rhythm of RLS. However, the discriminative power of these measures would probably be reduced in comparisons with other sleep disorders or disorders related to abnormal motor function. Further studies are needed to show the differential diagnostic value of actometric nocturnal activity.

The benefit of analysing a sample of diagnostically pure RLS patients is that any actometric difference in comparison with the control group can now be expected to be due to RLS or RLS secondary effects such as insomnia. In theory, insomnia may have a direct effect on nocturnal activity, but not on the controlled rest-activity. To exclude the possibility that insomnia might explain the findings attributed to RLS, a further analysis was performed with a subgroup of RLS and control subjects with equal sleep initiation difficulties. In this analysis, the inter-group difference in nocturnal activity remained significant and the nocturnal activity still discriminated the RLS patients from healthy controls with no overlap. The control sample, mainly consisting of nurses working in shifts, did not represent ideal sleepers, although they reported no symptoms of major sleep disturbances on admission to the study.

A subsequent treatment intervention study (Tuisku et al. 2002b) with the same RLS patients further supports the value of actometric nocturnal activity and the controlled rest-activity as an adequate, quantitative measure of symptom severity. The treatment response to pramipexole, a drug with proven efficacy in RLS (Montplaisir et al. 1999), was objectively demonstrated as an 81% decrease of average nocturnal activity and a 68% decrease of average controlled rest-activity to the range of healthy controls. The decrease of both actometric parameters was significant. The subjective measures of symptom severity also decreased significantly, with the average decrease being 50%. Considering the results with this RLS sample and previous reports (Mills et al. 1993, Hening et al. 1999a, Montplaisir et al. 1999, Allen and Earley 2001), nocturnal quantitative actometry appears to be a more naturalistic, objective and quantitative assessment method for treatment trials than the previously used methods.

8.4. Akathisia-like hyperactivity in antisocial violent offenders with ADHD

The antisocial violent offenders with ADHD demonstrated motor hyperactivity at rest when compared with healthy controls. The lower limb motor activity in ASP with ADHD was lower than in NIA, but no significant difference was found in the ankle-waist ratio between the two patient groups. The emphasis of the hyperactivity was more on the lower limbs than on the trunk in both ASP with ADHD and in NIA. The majority of the ASP patients with ADHD demonstrated clinical akathisia symptoms (assessed by BARS) and a typical akathisia pattern in qualitative actometric analysis:

repetitive, rhythmic movement episodes of similar frequencies with a predominant occurrence of movement episodes at the end of the controlled rest period. The comorbidity between ADHD and RLS (Picchietti et al. 1999) suggests that the increased rest-activity in ADHD might be related to RLS rather than to akathisia. Qualitative analysis, however, gives evidence in favour of akathisia. The appearance of the NIA pattern and the increased movement indices in the ASP group are unlikely to be explained by psychopathology other than ADHD in ASP since current drug abusers were excluded and only three ASP patients were diagnosed with current affective and anxiety disorders. Their movement indices showed no significant differences in comparison with other ASP patients.

Aggressive behaviour is of primary clinical importance in ASP. The role of ADHD in antisocial development seems to central because conduct disorder, another precursor of ASP (McCracken et al. 2000), seems to be part of severe ADHD (Thapar et al. 2001). Furthermore, poor impulse control, an important prerequisite of aggressive behaviour, is an essential feature in both ADHD and conduct disorder (American Psychiatric Association 2000). The pharmacological treatment of aggression in ADHD includes the same options that are used in NIA, which suggests similarities in their pathophysiological mechanisms: aggression related to ADHD seems to respond to propranol and to clonidine (Mattes 1990, Pliszka et al. 2000), which are also the primary and secondary treatment option, respectively, in NIA (Taylor et al. 2001). As akathisia has been related to aggressive behaviour (Ratey and Gordon 1993, Stubbs et al. 2000) and akathisia-like motor findings have been observed here in violent offenders with ADHD, the possible role of akathisia-like mechanisms behind the aggressiveness of ADHD patients must be considered. Understanding the pathophysiology of akathisia may create new pharmacological hypotheses for treating aggression in ADHD.

The quantitative increase of rest-activity, in the absence of qualitative findings, would most naturally be related to ADHD itself, rather than to akathisia, because motor hyperactivity is an important diagnostic sign and a marker of symptom severity in ADHD based on the findings of this study placed in the context of previous studies (Halperin et al. 1992, Reichenbach et al. 1992). The qualitative finding of a rhythmic activity pattern may also be a primary feature of ADHD unrelated to NIA, despite the

apparent actometric similarities and clinical akathisia symptoms in BARS evaluation. Actometry proved to be more accurate than the normal clinical evaluation in detecting qualitative differences in movement patterns between the ASP/ADHD and NIA groups.

Not all the hyperactivity during rest can be attributable to akathisia in ASP/ADHD patients because these subjects also show a considerable amount of irregular, non-rhythmic activity, unlike NIA patients. The finding of a NIA pattern intermixed with an increased amount of non-specific activity suggests that two distinct phenomena explaining the quantitative increase of rest-activity may co-exist: general hyperactivity as the core symptom of ADHD and a more stereotyped activity related to akathisia. Independent of the underlying aetiology, the hyperactivity measured by actometry decreases with adequate treatment of ADHD (Porrino et al. 1983b), thus being an important indicator of symptom severity.

8.5. Abnormal motor activity in Asperger's disorder

For Asperger's disorder, no previous reports of objective quantification of motor rest-activity are available. The key finding in this study was the increased motor activity at rest and rhythmic movement patterns differentiating the Asperger's disorder patients from healthy controls. The detected hyperactivity appeared to be specific to the lower limbs since the ankle-waist ratio in the Asperger's disorder group was clearly higher than in the control group. These quantitative findings resembled the findings in NIA, and qualitative analysis revealed a rhythmic, periodic movement pattern similar to NIA in terms of frequency and timing. There were, however, clear differences between Asperger's disorder and NIA; the former exhibited less regularity of rhythm and amplitude, a smaller number of movement periods and more variation in movement patterns than the latter.

The majority of the Asperger's disorder patients were clearly hyperactive according to measurements, but two individuals fell within the range of the control subjects, showing very low activity. This may reflect the heterogeneity of our study sample, the heterogeneity of Asperger's disorder in general or two extremes on the spectrum of abnormal motor activity similar to the hyperactivity and hypoactivity reported in

autism (Gillberg and Billstedt 2000). The eight patients with increased motor activity also displayed qualitative similarities to NIA. Their clinical akathisia symptoms and actometric findings were inter-correlated, providing further evidence for the akathisia-like phenomena in Asperger's disorder. The finding of lower limb motor hyperactivity in Asperger's disorder cannot be explained by comorbid ADHD symptoms, as no correlation was found between WURS scores and activity levels, nor was there any difference between subjects with or without a history of ADHD according to WURS. Clinical RLS appeared in only one of the Asperger's disorder patients, offering no explanation for the motor hyperactivity findings.

Our results suggest mild, idiopathic akathisia in Asperger's disorder patients. The pathophysiology of NIA is related to D2 dopamine receptor occupancy of antidopaminergic drugs in the basal ganglia (Farde et al. 1992), but according to histochemical studies, the limbic, cingulate cortex is also involved in the pathophysiology (Ohashi et al. 1998). A dysfunction in these dopaminergic circuits may also be responsible for the neuroleptic intolerance in autism and Asperger's disorder, as there is already evidence of dopaminergic dysregulation, basal ganglia abnormalities and metabolic hypofunction of the cingulate cortex in autism (Jacobson et al. 1988, Ernst et al. 1997, Haznedar et al. 2000). The hypothesis of idiopathic akathisia in Asperger's disorder is further supported by the hyperactivity and irritability symptoms in autism which respond to clonidine (Jaselskis et al. 1992, Fankhauser et al. 1992), one of the treatment options in NIA (Adler et al. 1987, Miller and Fleischhacker 2000), and the clinical vulnerability to neuroleptic-induced movement disorders (Campbell et al. 1997, Scahill and Koenig 1999).

Instead of being a sign of idiopathic akathisia, the increased rest-activity may simply be a motor manifestation of a hyperactive subtype in autism (Gillberg and Billstedt 2000), and the rhythmic pattern may be a manifestation of stereotypic movement related to autism itself rather than to akathisia. It is also possible that the rhythmic, involuntary stereotypies encountered in neuropsychiatric disorders, including akathisia, all belong to the same continuum of clinical manifestations of basal ganglia pathophysiology (Tan et al. 1997). The akathisia-like hyperactivity in most patients and the hypoactivity in two patients, may be clinical correlates of akathisia and

hypokinesia of Parkinson's disease since there are parkinsonian features in autism (Vilensky et al. 1981).

8.6. Methodological questions

8.6.1. Controlled rest-activity

Controlled rest-activity seems to more specific an indicator of abnormal motor activity than the measurement of diurnal activity in hyperactive neuropsychiatric disorders, at least in NIA, RLS and ADHD. It also offers higher comparability than measuring diurnal activity because the environment and the situation is the same for all subjects during measurements of controlled rest-activity. The ideal time of day for measuring rest-activity, may not, however, be the same for all neuropsychiatric disorders, as they have different diurnal activity rhythms (Porrino et al. 1983a, Hening et al. 1999b, Poyurovsky et al. 2000). Variation in the recording time, on the other hand, reduces the comparability of different disorders. A possible association between time of day and the main differences between the groups when comparing Studies I-IV was controlled for by Spearman's correlation test, which showed no significant association between the time of recording and controlled rest-activity.

Time of day for actometric recording is especially important in RLS, in which the symptoms follow a specific diurnal rhythm. However, no correlation between recording time and activity level was found within this group, probably because the time of recording for all subjects and their controls in the RLS study was limited to within two hours. As both motor symptoms and subjective discomfort peak at midnight (Hening et al. 1999b), the recording time (5 pm-7 pm) may have led to an underestimation of motor hyperactivity in RLS patients. A later recording time of controlled rest-activity would thus have yielded a more dramatic increase of activity as compared with controls, but choosing a night-time recording instead of a day-time would have changed the naturalistic setting into an unnaturalistic one: it is more usual to sit in a medical interview during the daytime unless there is an emergency case. A night-time recording would also have reduced the comparability of RLS subjects with the other study populations. During the night, dopamine secretion is lower than during

the day, which probably would have an effect on rest-activity (Sowers and Vlachakis 1984).

The recording time at noon for NIA patients and their controls in Study I is not ideal either because NIA and other neuroleptic-induced EP movement disorders show a worsening of symptoms in the afternoon for an unknown reason (Poyurovsky et al. 2000). Thus, assessment during the first half of the day may lead to an underestimation of their severity (Poyurovsky et al. 2000). The ideal recording time for ADHD patients is unknown. In a naturalistic actometric study, these individuals displayed hyperactivity regardless of the time of day (Porrino et al. 1983a). In autistic disorders, even less information is available concerning the diurnal rhythm of motor activity, which may be related to problems of compliance and tolerance in these patients with long-term use of activity monitors (Hering et al. 1999).

The normal circadian activity recorded in healthy persons peaks in the afternoon (average acrophase at 2:50 pm) and is markedly attenuated between 11 pm and 7 am (Brown et al. 1990). There are, however, large variations in the activity phases between healthy individuals (Binkley et al. 1993). The main interest of this study was not diurnal activity rhythm, but the standardized day-time rest-activity in neuropsychiatric disorders with hyperactivity or other motor symptoms, although individual and population-specific diurnal activity rhythms may have had an effect on results.

The main methological aim of the study was to create as naturalistic and as standardized an actometric method to measure activity in physical rest as possible. Compared with previous diurnal and day-time activity recordings with ambulatory monitors, the controlled rest-activity method is more standardized, and compared with more accurate and more standardized laboratory studies, it is more naturalistic. The suggested immobilization test, created by Montplaisir et al. (1998) to measure motor symptoms of RLS by EMG, is based on the same idea as controlled rest-activity: to measure lower limb rest-activity while the patient is sitting still. The former is a more standardized method, but the setting is more unnaturalistic, and presumably limits the spontaneous movement of the subject in response to unpleasant leg sensations. In addition, the instructions given and the laboratory setting direct the attention of the

subject to the measuring procedure. As the EMG electrodes make direct skin contact with the subject in connecting him or her to a computer system by wires, they are likely to disturb the subject more than the ambulatory actometric monitors attached around the limbs on top of clothing.

A method, comparable with measuring controlled rest-activity in this study, which utilizes ambulatory actometry by applying it in a controlled and standardized setting, has been presented by Tulen et al. (2001). They quantified abnormal, involuntary movements of the head of patients with Tourette's disorder during a naturalistic interview and other situations. A standardized, controlled observation period has also been created by Fann et al. (1977) for accelerometric quantifying of the spontaneous motor activity during rest in TD patients. In this method, the subject is described to sit relaxed in a chair for evaluation of the resting condition, and the recording sites are ankles, wrists and chin.

In general, better standardization seems to be acquired at the cost of losing the naturalistic character of the study setting. Natural sciences applied to human subjects confront the eternal dilemma of a more generalizable, reductive approach or consideration of the natural specificity of the subject. Clinical studies in medicine often represent less standardised observation of the subject instead of using rigorously experimental, externally manipulated settings (Alanen 1989).

8.6.2. Comparability and properties of actometry

Actometric data obtained from different commercial applications are not comparable as the modulation, integration and recording of signals is different. The output data is generally referred to by the term "activity counts", which are not equivalent between different types of activity monitors (Gorny and Allen 1999). Even within the same type of actometric monitors, variations in the numerical activity counts and graphic output data may occur unless properly and regularly calibrated. This reduces the generalizability of actometric findings obtained with different activity monitors, and no "normal ranges" or "pathological ranges" can be given. Thus, the relative quantitative differences between groups are relevant and generalizable, but not the actual numerical values. Acceleration quantified as "activity counts" does not

represent an absolutely defined physical measure, or unit, and can be criticized for being an artificial, constructed quantity. Philosophically, however, all quantities can be considered as scientific, abstract constructions, which are merely used for measuring essential, non-quantitative qualities and relations of reality (Niiniluoto 1984).

Activity counts, although not representing exact units, can be approximately equalized to units of gravity. Future studies should seek to equate the output from the different monitors to a common unit of gravitational force so that all monitors can be more readily compared (Welk 2002). With the actometric method of this study, 1 g of gravitation roughly equals 106 activity counts when using the time window 0.1 s (Spiro 2002). The digital integration mode of data collection (see section 3.6.) in PAM3 type monitors used in this study allows the waveform of the movements to be virtually reconstructed, and unlike other methods, allows the amplitude of movements to be taken into account (Gorny and Allen 1999). The graphic output of the digital integration method is suitable for qualitative analysis of movements to, for example, diagnose low-amplitude, hypokinetic tremor or identify series of PLM. The digital integration method used in this study is the most recently implemented actometric method (Spiro and Spiro 2001).

The time window of activity monitors can be chosen according to its purpose. The smaller the time window, the higher the time resolution of the movement. Accelerations of the human body are typically less than 10 Hz (Welk 2002). The smallest time window available in PAM3 monitors (0.1 s) was chosen to be able to distinguish movements within the range of EP movement disorders (see sections 2.4.3.). Because of the limited memory capacity of these monitors, choosing a smaller time window shortens the maximal time of continuous recording (14.5 hours in PAM3 with this time window). In diurnal recordings, the activity rhythms are typically measured with a larger time window of 5 min (Binkley et al. 1993) or 15 min (Virkkunen et al. 1994), which is suitable for long-term quantification of motor activity. By contrast, the qualitative analysis of movement patterns requires use of a small time window with a higher frequency rate of measurement than the frequency of the motor phenomenon to be measured.

Within a study, the test-retest reliability of accelerometry in standardized settings seems to be good (Reichenbach et al. 1992, Moe-Nilssen 1998), and the abnormal movement patterns detected in NIA, for example, are reproducible (Rapoport et al. 1994). The lower limb rest-activity of RLS patients while sitting showed no significant differences between EMG recordings of two successive days (Hening et al. 1999b). In our study, the reliability of the measurements was not controlled for. A repeated nocturnal recording in the RLS sample might have been useful for adaptation, which is a usual procedure at least in more invasive sleep studies such as those using polysomnography. To answer the question of whether the possible disturbing effect of ambulatory monitors may have worsened the RLS symptoms, the subjective experience of symptom severity during the last two weeks and during the actometry (reported as VAS scores) were compared. No significant worsening of symptoms at the time of actometric recording was observed, which is in accordance with the comments of the patients about wearing the ambulatory monitors.

Random variation of accelerometric data can be divided into biological (intra-individual) and analytic variation related to recording process (Dale et al. 2002). The use of triaxial accelerometers and standardization of their position on a participant reduce the unwanted variability of the data (Welk 2002).

8.6.3. Assessment of clinical akathisia symptoms by BARS

BARS has been created and validated for clinical evaluation of DIA (Barnes 1989). It has established statistical properties and strong face validity in NIA (Cunningham Owens 1999). The use of BARS for purposes other than assessment of DIA is questionable. It was used in these four studies for clinical screening and assessment of possible akathisia symptoms in hyperactive disorders other than DIA. In these studies, the informational value of BARS lies in supporting the akathisia-like, objective actometric findings. The statistically significant differences in BARS scores between healthy controls and each of the patient groups in our studies do not necessarily indicate a clinical significance because the zero level of healthy controls compared with unspecific restless symptoms (scoring 1 in BARS global scale) easily produces a statistically significant difference between groups. The score 1 in the BARS global scale is defined as “questionable akathisia”. Score 2 indicates “mild akathisia”, which

is clinically more relevant. This score, however, does not require typical motor symptoms of akathisia, and thus, cannot be concluded to indicate akathisia in RLS, which may present with similar subjective symptoms and unspecific motor restlessness as described for score 2 (Barnes 1989). As the objective motor symptoms of akathisia were missing in both actometric and clinical assessment of RLS patients, it is reasonable to conclude that these individuals did not display akathisia despite the statistically significant increase in BARS scores.

The clinical significance of BARS in classical NIA fulfilling the diagnostic criteria of DSM-IV is indisputable, but the clinical significance may be reduced in atypical forms of neuroleptic-induced akathisia (see section 8.1.) and is probably reduced in other forms of akathisia. In the ASP/ADHD group, however, it is possible that BARS actually measured akathisia symptoms because a majority of the patients scored 2 or more and would have fulfilled the DSM-IV criteria of NIA except for neuroleptic exposure. The heterogeneity and small size of the Asperger group produces difficulties in interpretation of results, but those patients with clinical akathisia symptoms assessed by BARS also showed more actometric evidence of akathisia than those without. The use of BARS in assessment of hyperactivity symptoms other than NIA may be clinically relevant in some disorders (Barnes 2001), but scientific conclusions should be drawn with caution.

8.6.4. Characteristics of subjects

The representativeness of the NIA sample is limited to hospitalized patients diagnosed with schizophrenia spectrum disorders who were able to comply with the study procedures. During patient recruitment one NIA patient was excluded because of such severe NIA that he was unable to remain seated for the 30-min recording time. Another NIA patient was excluded, because he became so paranoid and agitated about the actometric monitors that he was not able to finish the interview. Thus, the most psychotic patients and those with the most severe NIA were not represented in this sample. The average clinical symptom severity assessment by BARS was 2.5, which is between mild and moderate akathisia. The most severe forms of NIA were probably unusual on the wards serving as recruitment channels since such patients typically receive immediate treatment for akathisia. Even if the differential diagnosis is

complicated, their psychomotor agitation is often quickly treated with benzodiazepines. The NIA patients of this study represented a symptom severity range from mild to marked akathisia. They may benefit more from diagnostic support and symptom severity monitoring offered by actometry than the more severe emergency cases. This sample was also selected with respect to comorbidity with parkinsonian side effects, which were excluded (see section 5.2.). The comorbid cases may represent another variant of akathisia with a different pharmacological profile (Fleischhacker et al. 1990, American Psychiatric Association 1997, Taylor et al. 2001).

The RLS sample did not consist of clinical patients, but readers of a monthly health journal, which served as the recruitment channel. The volunteering RLS patients were initially screened by a telephone interview for a preliminary check of inclusion and exclusion criteria. Of the 22 candidates invited to participate in the study, seven were excluded based on clinical examination; out of which three for purely somatic reasons, two for purely psychiatric reasons and two for both reasons. The somatic exclusions were hypertonia and migraine requiring immediate medication, recovery phase of meningitis and clinical orthopaedic problems. The psychiatric exclusions were depressive disorders and a cyclothymic disorder. Possible axis 2 diagnoses were also controlled for by SCID (First et al. 1997b), although they were not considered exclusion criteria. None of the RLS patients included in this study exhibited any personality pathology according to SCID assessment.

The recruitment channel of RLS patients may have skewed the male-female ratio, which was 1:14 in this study sample. This does not match the reported ratio in epidemiological studies, which ranges from equal prevalences to slightly higher prevalences in women (Phillips et al. 2000, Ulfberg et al. 2001a, 2001b). Family history was positive in at least nine of the patients, and the proportion of a hereditary compared with a non-hereditary form of idiopathic RLS was slightly higher than reported in a large population (Winkelmann et al. 2000). The recruitment channel may also explain the better health habits of RLS patients than their controls, who were mostly nurses working in shifts and possibly experiencing relatively high stress levels due to the increasing working load in health care. More cigarette smoking, alcohol consumption and caffeine intake was reported in the control group, but because of the

unreliability of subjective reporting and non-standardized collecting of data, no conclusions can be drawn. However, it is likely that unhealthy habits do not explain the hyperactivity findings in the RLS group. This sample of RLS patients is not representative of the general RLS population, as it is mostly female with healthy living habits, suffering from considerable and frequent RLS symptoms in the absence of psychiatric or somatic comorbidity.

The ASP/ADHD group is not representative of either ADHD or ASP alone, and furthermore, is likely to represent the most severe type of ASP due to a history of violent criminality. This group is quite representative of violent offenders undergoing a court-ordered mental status examination, as they are random, consecutive cases. Only one refusal and one exclusion because of prescribed teophyllamine medication were made in this sample of violent offenders. The history of heavy drinking, drug abuse and frequent, subclinical head traumas was so common in this sample that these factors are likely to have an effect on results. Comorbidity with substance abuse disorders and their sequelae cannot be avoided without ending up with an unrepresentative sample.

The group of Asperger subjects comprised patients of the Helsinki Asperger Centre who were recruited by their clinicians. This is a clinic to which patients with a tentative diagnosis of Asperger's disorder are referred from all parts of Finland for further neuropsychiatric examination to re-assess the diagnosis. Because of the strict exclusion criteria, the study sample is not a random sample of all diagnosed Asperger's disorder patients but consists of non-medicated patients with no need for current psychiatric or other pharmacological treatments. The representativeness of the sample may also be reduced by possible difficulties in identifying the disorder in basic health care systems. The skewed male-female ratio is in accordance with ratios reported in epidemiological studies (Gillberg 1998b).

The overall representativeness of healthy controls in this study is reduced by their recruitment channel: they were hospital employees including students, cleaners, technicians, social workers, office clerks, doctors and nurses. They may be healthier than the general population because of their exclusion criteria; however, their subjectively reported health was not systematically controlled for, except by

laboratory tests (see sections 5.2.-5.5.). The controls may have been more aware of the study purposes and the method of measuring controlled rest-activity than the patients.

The comparability between all the study groups is lowered by different age and sex distributions: the youngest were the Asperger patients (mean age 29.8 years) and the oldest were the RLS patients (mean age 50.3 years), while the mean ages of the ASP/ADHD sample (34.3 years) and the two NIA samples (33.3 and 34.5 years) fell between these extremes. There was a natural predominance of male subjects in the ASP/ADHD group (only males) and in the Asperger's disorder group (7:3), while females were over-represented in the RLS group (14:1). The different recruitment channels and exclusion procedures further reduce the validity of inter-study comparison.

The abilities and motivations of the subjects to communicate during the interview showed inter-group variability. Healthy controls and RLS patients communicated fluently and were very compliant in answering all questions posed by the clinician. This may have resulted in a lower stress level in these groups during the interview than in NIA, ADHD/ASP and Asperger patients, despite efforts to maintain a neutral, low-stress atmosphere for all subjects (see section 6.2.). Some of the Asperger's disorder patients, in particular, may have felt that the naturalistic setting of a clinical interview was nevertheless challenging because of their qualitative difficulties in social interaction (American Psychiatric Association 2000). They did seem, however, to be able to regulate eye contact and topics of conversation when necessary, and none reported an unwillingness to continue the interview or any subsequent adverse effects of the interview. A more considerable problem was their unresponsiveness to the efforts of the clinician to restrict the interview to selected topics and to follow a standardized structure. The course of the conversation in the interview seemed to be affected by both individual differences and inter-group differences of study subjects.

Another special group with respect to communication was the ASP/ADHD sample. Some of them found the clinical interview to be frustrating while simultaneously being interviewed frequently during the court-ordered mental examination, thus giving short, impulsive answers to the questions. Their status may also have affected

the reporting of their symptoms, and the retrospective evaluation of symptoms based on their capacity and motivation to remember may not have been very accurate. As most adult patients being evaluated for ADHD have not been psychiatrically evaluated as children, a recurrent problem is the retrospective diagnostics of childhood ADHD (Ward et al. 1993). ADHD symptoms fulfilling the diagnostic criteria must have been present in childhood in order to diagnose an adult patient with ADHD. In this study, however, a great amount of data from other informants and official papers had been collected during the court-ordered mental examination, which were available to confirm the history of ADHD.

8.7. Limitations of the study

The main limitations of this study include overlap of the subjects mainly due to a lack of controls fulfilling the study criteria (see section 5.6.), different recruitment channels for study patients and their controls (see sections 5.2.-5.5. and 8.6.4.), less systematic exclusion procedures for controls (see sections 5.2.-5.5.) and their unconfirmed health status (see sections 8.3. and 8.6.4.), limited representativeness of the subject categories (see section 8.6.4.), study parameters affected by subjective reporting (see sections 6.4.-6.5.), methodological dilemma between standardization and maintaining the naturalistic character of the setting in controlled rest-activity assessment (see section 8.6.1.), poor generalizability of specific actometric findings (see section 8.6.2.), lack of reliability measures (see section 8.6.2.), application of BARS in populations, for which it is not validated (see section 8.6.3.), non-controlled factors possibly affecting motor activity, such as intake of nicotine and caffeine and thyreoid function (not controlled for in RLS patients and in most of the controls), subclinical affective and anxiety pathology (not systematically controlled for in healthy controls and NIA patients) and personality factors (not controlled for in healthy controls and NIA patients).

9. CONCLUSIONS

The results show abnormal rest-activity in each of the neuropsychiatric disorders of this study. Quantitatively, the activity is increased, and qualitatively, it is different from the rest-activity of healthy controls. Controlled rest-activity seems to be more

specific as a measure of abnormal motor function than diurnal activity in hyperactive disorders. Controlled rest-activity measured by actometry can be used as a diagnostic marker and a measure of symptom severity in NIA. The diagnosis and assessment of NIA has previously relied on a clinician's subjective evaluation. More objective methods should be applied in clinical trials, which form the basis of treatment guidelines and reimbursement decisions concerning drug treatments. The motor component of NIA can be easily and objectively monitored in treatment trials and in clinical practice by measuring controlled rest-activity with non-invasive actometric monitors.

Combining the quantitative and qualitative results in RLS with earlier findings (Montplaisir et al. 1998), the RLS patients are concluded to demonstrate a considerable amount of lower limb motor hyperactivity at rest, both awake and asleep, which is not accounted for by the PLM phenomenon. This apparently non-specific activity would most naturally be explained by the paresthesias and dysesthesias of the lower limbs causing an urge to move, an essential diagnostic feature of RLS. Motor restlessness, itself, is also an essential diagnostic feature of RLS (IRLSSG 1995). In the absence of reliable, objective assessment methods, the actometric recording of nocturnal lower limb rest-activity offers an option for measuring symptom severity and for supporting a diagnosis of RLS. The benefits of this method are 1. simple home recording with minimal disturbance of the subject, 2. good discriminative qualities, 3. an objective, quantitative measure of motor activity and 4. inclusion of the restless movements which are a response to subjective, sensory symptoms essential to the diagnosis.

Considering the previous studies (Halperin et al. 1992, Reichenbach et al. 1992, Teicher 1995, Dane et al. 2000), the increased rest-activity in adult ASP patients with ADHD is an important objective sign of residual ADHD symptoms and a useful measure of symptom severity. The abnormal rest-activity of Asperger patients was here objectively demonstrated for the first time. The quantitative and qualitative findings suggest the importance of careful evaluation of motor abnormalities in Asperger's disorder, which may be helpful in defining the subtype and the severity of motor symptoms. The findings in ASP with ADHD and in Asperger's syndrome suggest idiopathic akathisia in these developmental disorders, which may be

explained by the dopaminergic dysregulation in both ADHD (Lou et al. 1989, Lewy and Swanson 2001) and Asperger's disorder (Jacobson et al. 1988, Ernst et al. 1997). The pre-existing akathisia-like activity in these disorders indicates special pharmacological consideration should be given when prescribing drugs which may induce akathisia since akathisia may aggravate the aggressive, dysphoric and hyperactive symptoms of Asperger's disorder and ADHD. Besides idiopathic akathisia, this activity pattern may also represent a more common phenomenon of basal ganglia-generated stereotypic movements encountered in several neuropsychiatric disorders including ADHD, autism and akathisia (Tan et al. 1997).

Measuring motor activity offers a narrow but objective window to assessment of symptom severity and pathophysiological mechanisms of neuropsychiatric disorders. Measuring rest-activity by ambulatory activity monitors provides a useful and naturalistic assessment method. The instrumental measurements, however, give limited information on symptom severity. The impact of motor symptoms on the patient's daily life and functioning, which is of primary clinical importance, cannot be measured by actometry. Technical measurements also lack the aspect of subjective experience and suffering of the patient, which is fundamental in all psychiatric care. Combining this objective, quantitative assessment with the more traditional psychiatric evaluations will offer an integrative approach to meet the current needs of neuropsychiatric care and research.

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