Motor problems in Children with ADHD and clinical effects of Methylphenidate as assessed with the MFNU

by
Liv Larsen Stray

Thesis submitted in fulfilment of
the requirements for the degree of
PHILOSOPHIAE DOCTOR
(PhD)

Faculty of Arts and Education

University of Stavanger
N-4036 Stavanger
NORWAY
www.uis.no

ISBN 978-82-7644-393-6
ISSN 1890-1387

CONTENTS

1. Acknowledgements

There are many people I wish to thank for having made this thesis possible.

- The children, their parents and teachers/preschool teachers who have participated in both tests at the Resource Centre and in general research work.
- Professor Bjørn Ellertsen, who based on his many years of experience with clinical neuropsychological exploration of ADHD, motivated me to start the project and supervised my research and the writing process. With his professional competence and commitment he has been of crucial value to the realization of this thesis.
- My husband, colleague and research co-worker, clinical psychologist Torstein Stray, for contributing both as discussion partner on the theoretical questions associated with the connection between motor problems and ADHD and as "consultant" with regard to the technical work involved. Without our daily discussions and his support during the writing process, this work could not have been accomplished
- My colleague chief physician Anne Ruud for the fact that she discovered the clinical significance of MFNU in the diagnostic assessment of children with ADHD at an early stage and for being a co-worker and central participant in the research work leading to this thesis.
- PT and dr. philos Synnøve Iversen, with her combination of clinical and theoretical background, has contributed to highlight and clarify significant factors in the procedures for the MFNU manual as well as in the DVD. She has been both a co-worker and supervisor in the works on the thesis.
- Professor Finn Egil Tønnesen, The Reading Centre, University of Stavanger, who has been my statistics supervisor and who has contributed to the writing process with encouraging discussions and recommendations.
- Professor emeritus Thorleif Lund, University of Oslo for methodological advices and inspiration.
- The Reading Centre at the University of Stavanger, for valuable help, encouragement and support trough the process, and for publishing the MFNU user manual. In particular Astrid Engelsgjerd

for her help in practical matters and for making me feel at home at the centre as well as Jostein Tollaksen and Ellen Rafoss for practical help.
- The Sørlandet/Birkelid Resource Centre, particularly the former director Ole Petter Olsen, for supporting the research and for funding the rating of videos.
- Department of Child Psychiatry, Sørlandet Hospital, Norway, especially its director of many years, Karl Erik Karlsen, for giving me the opportunity to perform the research at the department.
- My former colleagues at the Birkelid/Sørlandet Resource Centre, for providing a creative working place with rewarding discussions and practical help during the development of the MFNU.
- My colleagues at the Department of Child Psychiatry (ABUP) in Kristiansand and Arendal for support and challenging discussions.
- Iris Olsen, leader of the research unit of ABUP for moral and practical support.
- The Unit for Research, Development, and Innovation, Sørlandet Hospital for funding online submittance of two of the articles and Svein Gunnar Gundersen and Sissel Ledang, leaders at the research department at the hospital, for their support.
- Dr. Sandrine Schuhler Slotten for language advices.
- Chief physician Kirsten Djupesland and Torunn Tjore, Sørlandet Hospital for their practical help and participation in the research.
- Physiotherapist Karen Storaker for participation in the scoring of videos, and for challenging discussions during the development of the MFNU.
- Co-writers of Paper IV, chief physician Per Vesterhus, neuropsychologists Peter Arnesen and Stephane Vildalen for challenging discussions.
- Chief physician Elisabeth Øynes, for discussions and support regarding the practical use of the MFNU, for giving lectures in MFNU to child psychiatrists and for letting me participate in these.
- Department of Physiotherapy Science, University of Bergen, Norway and professor Elisabeth Ljunggren for initiating the research process.
- All the physiotherapists who directly and indirectly have participated in the development of the MFNU in the development of the manual and in assessment of interrater agreement.

Acknowledgements

- All the physiotherapists, physicians and educators around the country who in various ways have contributed with their comments after having piloted the MFNU.
- The staff of the schools in the municipality of Songdalen, Norway
- Masters in Special Education Siri Grønness, Eivind Herlofsen and Anne-Grethe Ørsland, for challenging discussions and for providing examples from their daily work, illustrating how the motor problems affect the daily living of children with ADHD and how the teacher's knowledge of such problems can make a difference for the child.
- Photographer Per Moseid for filming most of the videos used on the DVD.
- My children Atle, Ingunn, Torje and my daughter-in-law Amanda for technical and language support.

My thanks go out to all of you.

2. List of papers

This doctoral thesis is based on the following:

Stray, L. L., Iversen, S., Stray, T., Ellertsen, B., & Ruud, A. (2006). MFNU - Motorisk Funksjonsnevrologisk Undersøkelse Brukermanual med DVD. Stavanger: Universitetet i Stavanger.

Paper I. Stray, L. L., Stray, T., Iversen, S., Ellertsen, B., Ruud, A., & Tønnessen, F. E. (2009). The Motor Function Neurological Assessment (MFNU) as an indicator of motor function problems in boys with ADHD. *Behav Brain Funct, 5*(22).

Paper II. Stray, L. L., Stray, T., Iversen, S., Ellertsen, B., & Ruud, A. (2009). Methylphenidate improves motor functions in children diagnosed with Hyperkinetic Disorder. *Behav Brain Funct, 5*(21).

Paper III. Stray, L., Ellertsen, B., & Stray, T. (*Submitted*) Motor function and Methylphenidate effect in children with ADHD.

Paper IV. Ruud, A., Arnesen, P., Stray, L. L., Vildalen, S., & Vesterhus, P. (2005). Stimulant medication in 47,XYY syndrome. *Dev Med Child Neurol*, *47*, 559-562.

3. Summary

The Motor Function Neurological Assessment (MFNU) has been developed over a 25 year period based on clinical observations and assessments of children referred for evaluation of possible Attention Deficit Hyperactivity Disorder (ADHD)/Hyperkinetic disorder (HKD). The sub-tests of the MFNU were constructed to demonstrate these motor problems to parents and teachers of these children, and to make changes in motor performance observable when the child was medicated with Methylphenidate (MPH, Ritalin©). The reliability and usefulness of this instrument as a clinical assessment tool has been demonstrated through many years of clinical practice with hundreds of children at the Birkelid Resource Centre prior to the start of the research. However, the MFNU was not originally constructed as a research tool. Since the usefulness of the instrument in this respect is of crucial importance to the validity of our research findings, much effort was put into development of a user manual and DVD with precise instructions for test administration on each subtest, together with rules of interpretation and scoring.

The aim of the research projects was to investigate possible relationships between ADHD symptoms and certain motor problems observed in children with this diagnosis.

The first research question of our studies, using the MFNU as our research tool, was to establish to what extent the MFNU discriminates between children with and without ADHD. In the first study 25 drug-naïve boys, aged 8-12 years and recently diagnosed as HKD F90.0, and 27 controls without ADHD participated. Highly significant differences between the groups were found on all the MFNU sub-tests. A high percentage of 'severe problems' was found in the ADHD group. The control group typically presented few, if any severe problems. When the 'moderate problems' and 'severe' scores were combined, the ADHD group presented problems within a range of 80 to 96%.

The second research question was to investigate the effect of MPH on motor problems in children with ADHD. Twenty-five drug-naïve boys, aged 8-12 years and recently diagnosed as HKD F90.0 participated. A double-blind, placebo controlled, cross-over design was applied, using MPH or placebo capsules. The children were assessed individually with the MFNU twice a day on two different days, with at least one day

interval. The first trial each day was baseline and the second was the experimental condition. Significant improvements were found on all sub-tests when comparing Baseline to the MPH trial. A Cohen's *d* of 1.27 was found, applying 'Total score' from the MPH and the Baseline trials. The most pronounced improvements with MPH compared to Baseline were observed on sub-tests assessing high muscular tone.

The third research question was to investigate to what extent motor problems are present in positive responders to MPH on their core behavioural problems of ADHD, compared to non-responders. The study group consisted of 73 children. They were retrospectively divided into two sub-groups based on their response to MPH on their core ADHD problems: 'Medicine responders' and 'Non medicine responders'. Highly significant differences were found between the groups on MFNU sub-tests and the 'Total Score'. The responder group obtained a significantly higher median score than the nonresponder group on all sub-tests. No significant gender or age differences were found in the responder group, nor in the nonresponder group, on any of the MFNU sub-tests.

A case study describes changes in motor function on MPH medication in children who did not fully satisfy the ADHD criteria, but were positive medicine responders. The two children were diagnosed with 47, XYY syndrome. The MFNU served as an important supplement in the evaluation of MPH treatment in these children. This shows that the MFNU is valuable in assessment of other syndromes than ADHD.

We have shown that the MFNU is a sensitive instrument in the assessment of motor inhibition and high muscle tone in trunk, shoulders, hips and legs in boys with ADHD-C/HKD. The results from the research presented in this thesis support our clinical observations regarding specific motor problems in children with ADHD. We found such problems both in the diagnostic group in general and in children with ADHD, who respond positively to central stimulant medicine, in particular. A single dose of MPH in boys diagnosed as ADHD-C yielded a significant improvement of the motor problems. There was a corresponding weaning effect after the metabolisation of the MPH which is very similar to what is seen in the behavioural symptoms of the syndrome. The results support our suggestion that there may be a close relationship between the motor problems measured by the MFNU and the neurofunctional causes of ADHD.

The MFNU is still in need of further validation research, particularly regarding the use in diagnostic assessment.

.

4. Introduction

4.1. Background of the thesis

This Thesis is a product of 20 years of observations and assessment of children with attention and hyperactivity problems and children with learning disabilities. This was done at the Birkelid State Resource Centre for Special Education, Norway, which at that time was one of several Governmental Centres for special education. It is also a product of clinical assessment of children with ADHD at the Department of Child and Adolescent Psychiatry, Sørlandet Hospital, Norway. Being a physiotherapist and part of an assessment team consisting of clinical psychologists, physicians, educational staff, nurses and social workers, my focus has been on the motor problems very often presented by these children in daily life and educational settings. Several of the children who were later diagnosed as Attention Deficit Hyperactivity Disorder (ADHD) showed characteristic motor difficulties in these situations. However, few or no problems were found in many of these children when they were assessed with the quantitative part of the Movement Assessment Battery for Children (M-ABC), the Function Neurologic Assessment (FNU) (1), somatic and neurological assessments or standard neuropsychological testing (2).

Although motor problems in children with ADHD are well known, our clinical observations indicated a higher prevalence than the 50% reported earlier (3, 4). In my experience it was a common observation among teachers and other professionals that many children with ADHD are normal or high achievers in activities and sports characterized by speed, as for example snowboarding and downhill skiing. On the other hand, when the children demonstrate ”being fidgety” and restless, repeatedly slide down his/her chair or ”hangs” over his desk in the classroom, these actions were often understood as active disruption, inattentiveness or “laziness”. In the process of developing the Motor Function Neurologcal Assessment (Undersøkelse) battery (MFNU) during the 1990-ies it became apparent that much of this behaviour could be understood as problems related to regulation of muscle tone and the maintenance of body stability. The construction of the MFNU was primarily motivated by the need to demonstrate these characteristic motor problems in a systematic way to parents and teachers. With a steadily growing number of children being assessed with the MFNU it

became clear that motor problems among children with ADHD revealed by the test were much more common than expected.

Important observations were also made in connection with the testing of central stimulant medication performed as part of the assessment of ADHD at the Resource Centre, in cooperation with Departments of Paediatrics and Child Psychiatry at Sørlandet Hospital. The children who showed positive effect of Methylphenidate (MPH, Ritalin©) on their core problems of ADHD also showed marked motor improvement when tested with the MFNU. Growing clinical experience also indicated that the children with the highest scores on the MFNU were the best responders to MPH.

The empirical studies presented in this thesis were aimed at scientific verification of the clinical observations referred above. A user manual, with an accompanying DVD (5) served as background material and a guide to the detailed instructions and scoring system applied in the studies.

4.2. THE DIAGNOSIS OF ADHD/HKD

> *"Any diagnosis represents only a summary of diagnosticians' knowledge at a certain time and as new knowledge is acquired, diagnostic criteria will be altered." (Sagvolden & Archer, (6))*

Children with ADHD represent a heterogeneous population which displays considerable variation in symptoms. It is a prevalent child psychiatry disorder which lasts into adolescences and adulthood for many persons affected. A high proportion of children with ADHD will experience school failure and develop conduct disorders, delinquent behaviour and antisocial behaviour. As a result, the burden of the disorder to affected individuals, their families and society is considerable (7). Different diagnostic traditions, i.e. the manuals of The Tenth Revision of the International Classification of Diseases (ICD-10) (8) and The Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (9) have developed rather different diagnostic criteria. The label ADHD is often used both for the DSM-IV diagnosis of AD/HD and for the more restrictive ICD-10 diagnosis of Hyperkinetic disorder (HKD). Therefore, the prevalence may differ between studies. The process of arriving at the definitions of ADHD and HKD has been complex. The diagnoses are made on the

basis of subjective reports, mostly from parents and teachers. Objective psychological or biological criteria have not yet been established. The ICD-10 and the DSM-IV recognize the same 18 symptoms of HKD and ADHD; nine inattentive and nine impulsive and hyperactivity symptoms. Symptoms have to be present in two or more settings and there has to be clinically significant impairment in social, academic or occupational functioning (10).

Inattention:
1. Fails to attend to details
2. Has difficulty sustaining attention
3. Does not seem to listen
4. Fails to finish tasks
5. Has difficulty organizing tasks
6. Avoids sustained effort
7. Loses things
8. Is distracted by extraneous stimuli
9. Is forgetful

Impulsivity and Hyperactivity:

Impulsivity:

1. Blurts out answers
2. Difficulty awaiting turn
3. Interrupts or intrudes on others
4. Talks excessively (ICD-10)

Hyperactivity:

4. Talks excessively (DSM-IV)
5. Fidgets with hands or feet
6. Leaves seat in classroom
7. Runs about or climbs
8. Difficulty playing quietly
9. Excessive activity

Some of the symptoms have to be present before the age of 7 years in DSM-IV(9) and before age 6 years in ICD-10 (8). The ICD-10 requires the presence of symptoms of both impaired attention and overactivity while the DSM-IV does not. The diagnosis of HKD is restricted in the presence of other disorders like mood or anxiety disorders, and there is a separate category for the most prevalent comorbid condition (Hyperkinetic conduct disorder) (8). DSM-IV allows comorbid conduct

disorder as well as other psychiatric diagnoses (9). A text revision of DSM-IV was published in 2000 and many of the changes in the DSM-IV-TR concerning ADHD highlighted differences among the sub-types (11). The ADHD diagnosis of DSM-IV-TR is divided into 3 sub-types:

- Attention-Deficit/Hyperactivity Disorder, Combined Type (ADHD-C): if both criteria for inattention and hyperactivity–impulsivity are met for the past 6 months.
- Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type (ADHD-I): if criteria for inattention is met but criteria for hyperactivity–impulsivity is not for the past 6 months.
- Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive–Impulsive Type (ADHD-HI): if criteria for hyperactivity–impulsivity is met but criteria for inattention is not for the past 6 months (12).

In the following only the term DSM-IV will be used.
The prevalence of ADHD using the DSM- IV criteria is estimated to be 5–10% and of HKD, using the restricted ICD-10 criteria, 1-2% in the general population (10). The disorder is relatively stable over time and persists throughout adolescence and into adulthood in more than 50% of the cases (13). A substantially higher percentage of boys than girls are referred to psychiatric clinics for assessment of ADHD (14). Russel Barkley states that "…boys are three times more likely to have ADHD than girls and six to nine times more likely than girls to be seen with ADHD among clinic-referred children." (15).

4.3. ADHD – Neurobiologically based

Although the diagnosis of ADHD is based on behavioural criteria only, there is general agreement that the condition is primarily neuro-biologically based (16, 17). Family, adoption and twin studies have provided compelling evidence that genetic factors contribute to a substantial proportion of the variance in ADHD (17).

4.3.1. Neuropsychology of ADHD

A number of studies of children with ADHD have shown deficits on neuropsychological tests (18, 19). They have demonstrated poor inhibition responses and longer stop-signal reaction time when

compared with normal controls (19, 20). Different theoretical approaches have been developed to account for these empirical findings. Barkley (18) has proposed that poor behaviour inhibition is the core deficit of ADHD and that attention deficits are secondary to these. Sergeant (21) does not support the hypothesis of behavioural inhibition. He characterized the core deficit of ADHD as an activation deficit that selectively affects output stages rather than input stages of information processing. Johansen and Sagvolden (22) suggested that slow extinction of previously reinforced behaviour is an alternative explanation for the frequently observed excessive behavioural output that others have interpreted as "disinhibition". Altered dopaminergic function may play a crucial role in ADHD through failure to modulate nondopaminergic (primarily glutamate and GABA) signal transmission appropriately (23).

4.3.2. Neuroanatomy of ADHD

Magnetic Resonance Imaging (MRI) studies support the idea that a distributed circuit that includes the right prefrontal cortex, the caudate nucleus, the cerebellar hemispheres and a sub-region of the cerebellar vermis, is of importance in ADHD (17). Prefrontal mediated dysfunctions resulting in difficulties with impulse/inhibition control and self-regulation associated with higher order executive functions have been reported (24, 25). Castellanos (26) focused on the dopamine input from two midbrain systems (the ventral tegmental area and the substantia nigra) and described the complex basal ganglia circuits, emphasizing the direct input to the cortex from dopamine cell bodies in the first system and the regulation of the striatal–thalamic input to the cortex by dopamine cell bodies in the substantia nigra in the second system. He suggested that a dopamine deficit in the former and a dopamine excess in the latter system comprise a possible biochemical basis for ADHD.

Functional MRI in children with ADHD during a resting state has shown altered brain activity in the right inferior frontal cortex, left sensorimotor cortex, bilateral cerebellum and the vermis as well as in the right anterior cingulate cortex, left sensorimotor cortex, and bilateral brainstem (27). Berquin et al. (28) showed a reduced volume of cerebellar vermis in boys with ADHD and linked deficits in motor inhibition to dysfunctions in the cerebellum. Similar findings have been reported in girls with ADHD (29). Central nervous activation problems relating to the reticular formation have also been reported (13, 30).

4.3.3. ADHD and treatment with stimulant medication

The primary treatment of ADHD is central stimulant medication. A number of studies show that approximately 80% of subjects with ADHD show clinically significant benefits from treatment with central stimulant medication like Methylphenidate (MPH) or D-amphetamine (31, 32). Most children with combined-type ADHD respond well to both drug types, with rapid decrease of behavioural symptoms starting about 30 minutes after oral administration and peaking after 60–90 minutes (33). MPH, the drug that is most commonly used to treat ADHD, blocks the reuptake of dopamine and norepinephrine (NE) (17). Dopamine and NE are two out of four main neuromodulators in the brain (34)

4.4. Motor functions

A normal motor function is a result of coordinated processes of neurological, physiological, muscular and visuo-motor systems. Cognition, physical, emotional and environmental factors are also of importance (35). The anatomy and the functions described in the following, which are not specifically referred to, are retrieved from the Tantorski's functional Neuroanatomy (36) and Carlson's Physiology of behaviour (37).

4.4.1. Central neuro-motor system

Neural circuits in the frontal association cortex are important for the planning of movement. This planning is based on information received from the posterior cortical association areas and the primary motor cortex executes the movements. It controls, through the lateral corticospinal system the hands and fingers, through the rubrospinal system the arms and hands and through the ventromedial system the rest of the body. Apraxia (the "inability to properly execute a learned skilled movement" (Heilman, Rothi, and Kertesz, 1983, p. 381)) is caused by damage to the left parietal lobe, to the left prefrontal cortex, or to the anterior corpus callosum. Damage to the right parietal lobe can cause constructional apraxia, which is a difficulty in drawing or constructing objects. The basal ganglia play an important role in the control of movement. If they are damaged severe motor deficits will occur. This is seen in Parkinson's disease and Huntington's chorea. Their precise role is, however, not well understood. An important part of the motor system is the cerebellum. It controls head and eye movements and helps maintaining posture. The connections to frontal

motor areas enables the cerebellum to improve motor skills, in the same manner as they seem to be involved in mental and language skills (38). The cerebellum is also involved in control of the ventromedial system and in postural reflexes. It receives input from the vestibular system and projects axons to the vestibular nucleus. The cerebellum receives auditory and visual information, as well as kinesthetic information from the spinal cord. Cerebellum influences behaviour through the vestibulospinal and reticulospinal tracts, which are two of the three ventromedial pathways. Cerebellum is important in the coordination of movement, particularly the ability to conduct successive movements rapidly. Neocerebellar circuits are crucial for precise temporal relationships in motor responses (39). The cerebellum is involved in the control of the limb and hand movements. The cerebellum contains the neural circuitry needed to calculate the complex, closely timed sequences of muscular contractions that are needed for rapid, skilled movement, i.e. independent limb movements. These movements are initiated by the frontal cortex which controls neurons in the primary motor cortex. The cerebellum also receives information from the somato-sensory system about the current position and the movement of the limbs necessary for computing the details of movements.

Damage to the cerebellum will cause jerky, erratic and uncoordinated movements. Lesions of different regions of the cerebellum produce different symptoms. Disturbance in posture and balance is caused by damage in the flocculonodular lobe or vermis. Limb rigidity is a result of damage to the intermediate zone. Weakness and disturbance of movement (instead of smooth movements) is caused by damage to the lateral zone of the cerebellum. Such damage also impairs the timing of ballistic movements. A ballistic movement is a high-velocity musculo-skeletal movement, such as a tennis serve or boxing punch, requiring reciprocal coordination of agonistic and antagonistic muscles (40).

The reticular formation consists of a large number of nuclei located in the core of the medulla oblongata, pons, and midbrain. In the pons and medulla oblongata there are several nuclei which have specific motor functions such as respiration, sneezing, coughing, and vomiting. The reticular formation controls the activity of the gamma motor system and it regulates muscle tone. Muscle tone may be increased or decreased based on the balanced influence from inhibitory and facilitating regions of the reticular formation (41). The reticular formation is central in the control of posture through the ventromedial

pathways. Neurons from the reticular formation can activate a whole set of muscles at the same time, possibly as a modulator in the adjustment of the body's position in order to maintain balance. Reticulospinal fibres project to motor neurons which affect stabilizing muscles (proximal extremity muscles and muscles that stabilize the column) (42). They are of particular importance for the maintenance of upright posture, orientation of the body and head towards the surroundings and for certain gross movements of the limbs (41). The reticular formation is involved in motor inhibition (43) and locomotion is also influenced by this brain area. Regulation of the central nervous activation is partly connected to the reticular formation in the brainstem and partly to the amygdala. Activation is also supported by structures in the corpus striatum and basal ganglia (44).

4.5. Motor problems in children

Developmental Coordination Disorder (DCD) is a diagnosis in the DSM-IV system for a serious impairment of motor coordination that cannot be related to a medical condition (9). The children must present motor function significantly below chronological age and the motor impairment must interfere significantly with activities of daily living. The prevalence of DCD is reported to be 5-6% (9, 45). In the ICD-10 the similar diagnosis is labelled Specific Developmental Disorder of Motor Function (SDDMF). It includes clumsy child syndrome, Developmental Coordination Disorder and Developmental Dyspraxia (8). Although the classification of motor problems as DCD/SDDMF is common, some children may display motor problems which affect their daily living, but which can not be identified with traditional instruments.

4.5.1. Assessment of motor problems in children

Standardized tests like the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) (46), the Movement Assessment Battery for Children (M-ABC) (47) and the Developmental Coordination Disorder Questionnaire (DCDQ) (48) are often used for diagnosing DCD (49, 50). Neuropsychological tests like The Grooved Pegboard Test (2), the Maze coordination test (51), and the Finger-tapping test (2) as well as neurological soft sign assessment and the FNU (1) are often used to assess motor problems.

For newborn children and toddlers other methods are used to examine movement. Behavioural state, or "level of arousal", is generally considered to be a very important factor to monitor in studies of neonatal movement. Their postural behaviour and position in space have been related to level of arousal (52).

Crawford et al. (53) found that different tests identified different children, and that children may score within the normal range on one test of motor function, but found to be impaired on others. The MFNU was developed to specifically address motor problems in children with ADHD (54).

4.6. ADHD and motor problems

4.6.1. Motor problems in children with ADHD

The motor problems in children with ADHD have been described and discussed by many researchers (3, 35, 44, 55-59). An overlap of 30-50% has been reported between ADHD and DCD (45, 50). Pitcher et al (3) found that 58% of boys diagnosed as ADHD-I, 49.1% of boys diagnosed as ADHD-HI and 47.3% of those diagnosed as ADHD-C scored in the upper 15thpercentile on the M-ABC. Children with ADHD have been reported to have impaired handwriting (60) and impaired balance (61). Synkinesis (overflow of movement) has also been reported (57). Kroes et al. (62) found that qualitative domains of Dynamic Balance, Diadochokinesis and Manual Dexterity and a Total Qualitative Score were significantly associated with ADHD. Static Balance also tended to be associated with ADHD.

In the definition of HKD the ICD-10 states that: "Impairment of cognitive functions is common, and specific delays in motor and language development are disproportionately frequent" (8). There is currently no acknowledgment of motor problems within the differential diagnosis section for ADHD in the DSM-IV (9). The differential diagnoses section for the DSM-IV diagnosis 'Developmental Coordination Disorder' (DCD), states that "Individuals with Attention-Deficit-Hyperactivity Disorder may fall, bump into things, or knock things over, but this is usually due to distractibility and impulsiveness, rather than to a motor impairment" (9). Yet, it has been shown that poor fine motor ability found in children with ADHD could not be attributed to deficits in attention or concentration, but rather to factors relating to their motor ability (3, 63). Movements in children with ADHD are

jerkier and require more time than controls to change the direction of movement (64, 65). Kalff and collaborators (66) found that children at risk for ADHD were generally less accurate and more variable in their movements than children with psychopathology or control children.

4.6.2. ADHD, motor problems and stimulant medication

Harvey et al. (67) found that stimulant medication trials indicated no significant effect of central stimulant medication on the movement skill patterns of children with ADHD. Zeiner et al. (68) found that stimulant medication was associated with improvements on tests of sustained attention, working memory and motor steadiness. Lerer et al. (69) showed that administration of MPH improved handwriting in children with Minimal Brain Dysfunction (MBD). This term has been abandoned, but it is quite reasonable to assume that what is now termed ADHD was a significant part of it. In children with the combined DSM-IV diagnosis of ADHD and DCD Flapper et al. (70) showed that medication with MPH for 5 weeks improved handwriting and manual dexterity. Rubia et. al. (71) demonstrated improved motor timing in children with ADHD when medicated. MPH also improved speed of inhibition and response execution processes (72). O'Driscoll et al. (73), assessing eye movements in children with ADHD, found that MPH improved motor planning and response inhibition. Rubia et al. (71) found that the persistent, but not an acute dose of MPH, reduced the variability of sensorimotor synchronization and anticipation. In contrast, our clinical observations have shown that a single dose improved movements. Some of the sub-tests of the MFNU were constructed to demonstrate this. In a pilot study on 6 children with ADHD, the MFNU showed that all children had motor problems, and that all children showed improved performance on most of the sub-tests when retested on MPH (54). We also observed that medication yielded no lasting improvement in motor performance on the MFNU. When retested without MPH the children typically showed the same motor problems as before medication. This pattern is very similar to the lack of lasting improvement seen in the behavioural symptoms of ADHD/HKD, when medication is withdrawn.

4.7. The MFNU

4.7.1. Background for the development of the MFNU

The MFNU focuses on motor problems in children with ADHD. It was developed during the 1990-ies at Birkelid Resource centre (54) in

close collaboration with well educated and specialized personnel trained within the fields of ADHD, learning and conduct problems. Diagnostic assessment of ADHD was carried out by multi-professional teams at the centre including clinical psychologist/neuropsychologist, test technicians, counselling teachers, social workers, a nurse, physicians and physiotherapists. In the process of developing the MFNU the motor assessment was recorded on video as part of the ordinary assessment of the children. The videos were edited and discussed between the team members. The assessment situation at the resource centre gave me a unique opportunity to perform motor assessments and to observe the children during motor activities in diverse settings, such as school and leisure time. Observations of the child in school included handwriting, sitting at the desk, participation in gymnastics, playing with toys and with other children, eating and dressing. The children often started movements in a correct manner, but encountered problems when the movements were continued over time. During handwriting, the child was often observed to fixate the shoulder, leaning on the underarm of the writing hand, lifting the whole arm and the pencil from the paper after writing some letters and using a lot of force performing the handwriting. Handwriting was often observed to be hard, uneven and discontinuous, with a mixture of small and large letters. The child often failed to catch a tennis ball with one hand and to kick the ball correctly when playing soccer. In the classroom we often observed that the child was ”hanging” over the desk with the head on the desk or supported by the hand, or sitting in other positions that required minimal effort. Many of the children appeared “stiff” in their body, and easily got out of breath in gymnastics when they performed activities which required expansion of the thorax in order to increase oxygen intake, for instance when jumping or running. The author interpreted motor problems observed in children with ADHD mainly to be due to motor inhibition problems and to increased tone in muscles used to maintain balance and an upright position, and not to motor problems in general. The team discussions and the observations described constituted the basis for the development of the MFNU.

4.7.2. Inhibition problems revealed by the MFNU

Some of the FNU sub-tests (1) were modified in order to identify motor inhibition problems. The dynamic balance sub-tests, two legs and one leg, were modified in order to reveal problems stopping ongoing movements and maintaining the balance while changing direction. In

the FNU the child (8 years or older) jumps sideway back and forth one time within two marked squares (two jumps each way). In the MFNU the child makes three jumps each way, and jumps back and forth three times without stopping. This modification of procedure improved the inhibition assessment. Another example of modification of a sub-test from the FNU is diadochokinesis of the upper limb. In addition to full supination-pronation movement, the MFNU emphasizes that the hand is held as an ”extension” of the lower arm. By focusing on this detail, inhibition problems of the supinator muscle were more easily observed. The MFNU sub-test ‘Reciprocal coordination’ emphasizes full extension of the hand and finger after clenching. Many children with ADHD have problems with this detail when movements are repeated. The MFNU ‘Thumb movement’ differs from the FNU sub-test ‘Finger opposition’ requiring abduction/extension movements of the thumb after each opposition. When this movement is performed repetitively the sub-test reveals an increasing tone in the thenar muscles in children with ADHD.

4.7.3 High muscular tone revealed by the MFNU

The “lifting of one limb” sub-tests in the MFNU (‘Lifting arm’ and ‘Lifting leg’) together with ‘Passive movement of hips’ address high muscular tone in movement muscles which can be used compensatory to maintain alignment of the column. A high tone in m. Latissimus dorsi, for instance as a result of excessive compensatory use of this muscle in maintaining the alignment of the column, may restrict movements of the shoulder and may cause reduced mobility of the thorax. This may result in restriction of respiration and lead to shortness of breath.

The m. Latissimus dorsi is illustrated in Fig. 1.

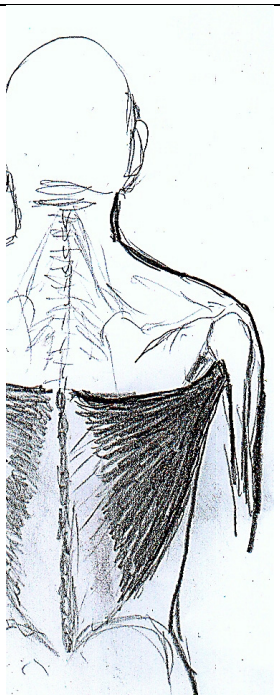


Fig. 1. M. Latissimus dorsi

The Psoas muscle is one of two muscles of the m. Iliopsoas. It attaches to the column, transverses the pelvic and attaches to the leg (trochanter of Femur) (74). When the m. Iliopsoas (see Fig. 2) is actively used in maintaining alignment of the lower column, restricted movements of the hip may occur. The MFNU sub-test ’Passive Movement of Hip’ reveals such restriction.

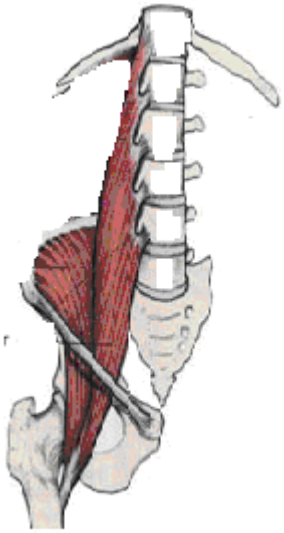


Fig. 2. M. Iliopsoas

A high tone in Sacrospinalis (Erector spinae) when used in order to maintain an upright position may cause reduced mobility of the thorax and restrict the respiration. The sub-test 'Palpation' in MFNU consists of palpation of m. Longissimus, m. Latissimus dorsi as well as examination of the mobility of the thorax'. The high tone in m. Longissimus is easily felt by parents, and comments like "it feels as if it is made of bone" have often been heard. High muscular tone is also found using the sub-test 'Passive movement of the foot'. The gastroc-soleus muscle group is active in maintaining and adjusting alignment (74), and a high tone may affect this adjustment and thereby the balance.

4.7.4. Inhibition problems, high muscle tone and daily living

Inhibition problems in muscles may affect fine motor activities that are part of handwriting and gross motor skills like ball activities. High muscular tone in Iliopsoas may reduce the extension of the hips which again may affect running and jumping. For some children a high tone in m. Iliopsoas may make the pelvic-tilting and the use of abdominal muscles in bowel pressure difficult. This may result in encopresis (75). Encopresis is found to be more common in children with ADHD than in controls (76) indicating a high muscular tone in their m. Iliopsoas. A high tone in the calf muscles may restrict the movement of the foot and

affect walking, running, jumping, kicking a ball, etc. It may also affect balance. Many parents have told us that they easily hear the differences between their child with ADHD and the siblings walking down the stairs. Complains by the child of stomach-, back- and neck-pains are also commonly reported by parents and teachers.

4.7.5. Sub-tests and scoring of the MFNU

The MFNU was initially named Modified Function Neurological Assessment (54). Although there were similarities, the assessment was very different from the FNU, which is a much broader assessment of both motor and sensory problems. Therefore the name was changed. For a short time the term Motor Assessment Battery was used, but the abbreviation MAB was too similar to the M-ABC and was therefore abandoned. Because all the sub-tests were motor sub-tests, the name Motorisk funksjonsnevrologisk undersøkelse (MFNU) (in English Motor Function Neurological Assessment) was chosen (5). The sub-tests of MFNU presented in Table I are from Paper I and II. This includes the sub-tests 'Throw ball' and 'Catch ball' which were later removed from the MFNU. In Paper III, only five out of these 17 sub-tests were used.

MFNU is not a test assessing motor problems in general. It is constructed to show motor problems in areas that we commonly have observed in persons diagnosed with ADHD. The sub-tests of MFNU were primarily chosen and designed to make visible particular motor problems to parents and teachers of children with ADHD. The purpose was to clarify how these problems might affect daily life activities and the child's interaction with others negatively. Practical issues, e.g. that all sub-tests could be completed in a reliable manner in a test situation which required little equipment and space, were also important in the final choice of sub-tests. In order to focus the attention of the child, the MFNU is performed in a "dynamic" and interactional way with no limits concerning time and number of attempts (5, 54). The child may also be offered practical help in order to ensure understanding of how to perform the sub-tests.

Table1

The sub-tests of the MFNU used in in Paper I, II and IV

Name of sub-tests	Description
01. Dynamic balance-2 legs	Three sideway jumps within marked squares, back and forth. The entire process is repeated three times without stopping.
02. Dynamic balance-1 leg	Three sideway jumps on one leg within marked squares, back and forth. The entire process is repeated three times without stopping. Both legs are tested.
03. Diadochokinesis-right 04. Diadochokinesis-left	Pronation-supination of one hand, the elbow flexed 90 degrees. The hand is held as an ”extension” of the lower arm. The exercise is performed for approximately 15–20 seconds.
05. Reciprocal coordination	Alternate clenching of one fist, and stretching of the other in a rhythmic manner, for about 15 seconds. Fingers should be nearly completely extended after the hand has been clenched. Elbows at a 90 degree angle, palms facing upwards.
06. Thumb movement	The tip of the other fingers are successively touched with the palmar surface of the tip of the thumb. After each opposition the child extends and abducts the thumb. Both hands are tested for approximately 20 seconds.
07. Throw ball	The tester plays ball with the child. A fairly large ball is used. The child has to throw with dominant arm in an upwards position. Shoulder movement is scored.
08. Catch ball	The tester plays ball with the child. A tennis ball is used. The child has to catch the ball with one hand, fingers flexed, without touching the body.
09. Walking	Walking with toes alternately pointing outwards (“Chaplin”) and inwards, followed by walking on the outer foot rend (Fog's test) and inner foot rend.
10. Lifting arm	Lies prone, arms in a 45 degree angle from midline, lifting one arm with the palm of the hand facing the floor.
11. Lifting leg	Lies prone, spina iliaca anterior is touching the floor while lifting one stretched leg at a time.
12. ”Flying”	Lies prone, the arm in a 45 degree angle from midline, lifting head, arms and legs.
13. Passive abduction-right hip 14. Passive abduction- left hip	Lies supine. Tester holds the child's knee and hip in a flexed position. The tester stretches and flexes the leg to elicit a relaxation of the hip muscles, and abducts the leg. The sides are evaluated separately.
15. Passive movement-right foot 16. Passive movement-left foot	Lies supine. Tester examines passive movement with dorsal flexion and eversion/plantar flexion of the right and left foot.
17. Synkinesis	'Synkinesis' is not a separate test, but an item for the evaluation of synkinetic movements registered in one or more sub-tests. When observed, the tester tries to correct it. The remaining synkinesis after correction is scored.

The MFNU uses a three categories scoring system: 0 = 'No problems', 1 = 'Moderate problems' and 2 ='Severe problems'. The sub-tests are scored according to the criteria presented in Table 2. More detailed criteria for each sub-test are presented in the MFNU manual and visualised in the accompanying DVD. The Total MFNU score is the sum of the sub-test scores. When we make a quantitative scale of qualitative attributes it will not capture the quality of movement and muscle consistency fully. The result of the MFNU must therefore be used together with clinical evaluation.

Table 2

Scoring criteria for the 17 subtests of MFNU

Score:		Criteria		
		subtests 01-12	subtests 13-16	subtest 17
0	'No problems'	The task is performed with no problems and little effort	Normal resistance against the movement is registered	Only sporadic synkinetic movements are registered
1	'Moderate problems'	The task is performed according to instruction, but with lot of attention and effort, or quality of performance is below what is expected for age	Resistance against the movement is registered	Moderate synkinetic movements are registered in one or more subtest
2	'Severe problems'	The child can not perform the task according to the instruction	Severe resistance against the movement is registered	Pronounced synkinetic movements are registered in one or more subtest

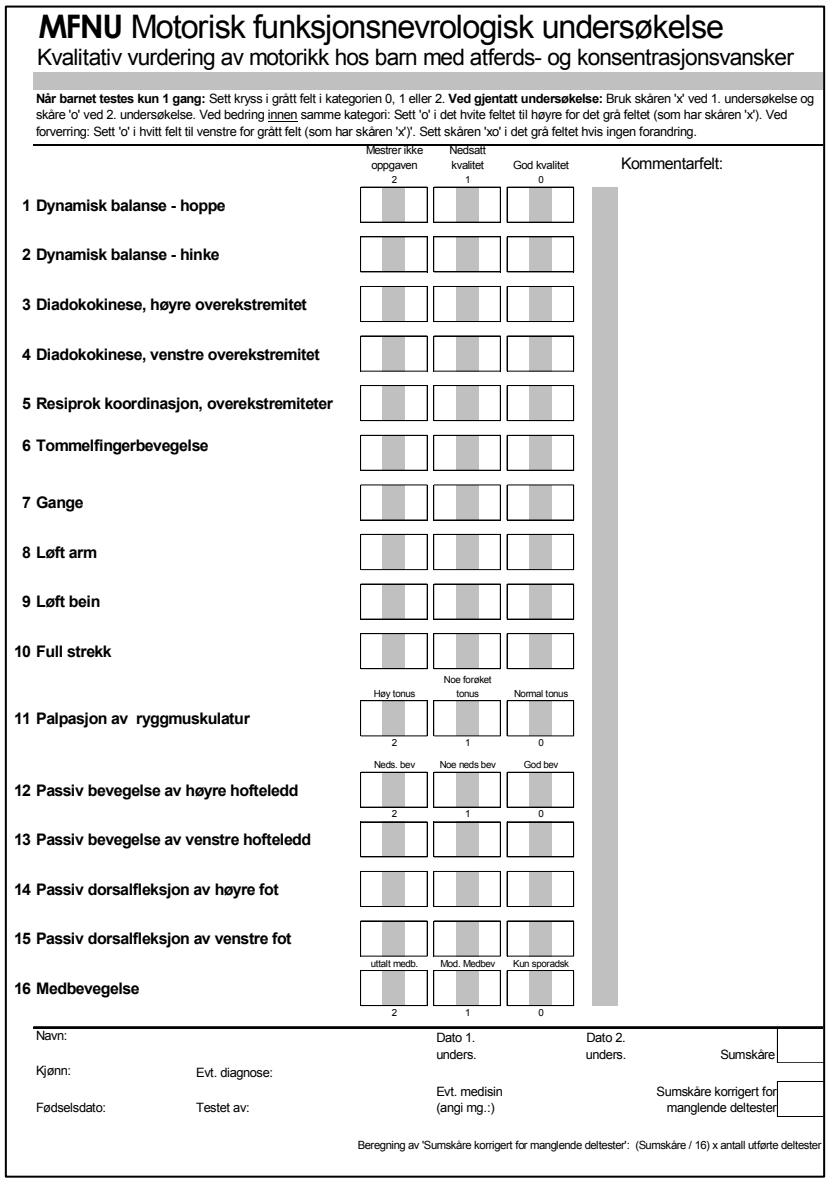
A scoring system based on observed changes in performance is used when comparing test-retest performances. A change score ranging form -3 to +3 is applied, where a score of '0' means no change. A score of '+1' or '-1' means that observable change in performance is registered, but not qualifying for a change across categories (see table 3). This scoring system permits a more subtle evaluation of change in performance than when the 3-category system is used repeatedly. In the MFNU user manual the change scoring system ranges from 1 to 7, with 4 as the neutral value.

Table 3

The change scores used in MFNU in test-retest procedures

	Change score
Neg. change across two categories	-3
Neg. change across one category	-2
Neg. change within same category	-1
No change	0
Pos. change within same category	1
Pos. change across one category	2
Pos. change across two categories	3

The MFNU scoring sheet is presented in Fig. 2.



MFNU Motorisk funksjonsnevrologisk undersøkelse

Kvalitativ vurdering av motorikk hos barn med atferds- og konsentrasjonsvansker

Når barnet testes kun 1 gang: Sett kryss i grått felt i kategorien 0, 1 eller 2. **Ved gjentatt undersøkelse:** Bruk skåren 'x' ved 1. undersøkelse og skåre 'o' ved 2. undersøkelse. Ved bedring innen samme kategori: Sett 'o' i det hvite feltet til høyre for det grå feltet (som har skåren 'x'). Ved forverring: Sett 'o' i hvitt felt til venstre for grått felt (som har skåren 'x')'. Sett skåren 'xo' i det grå feltet hvis ingen forandring.

	Mestrer ikke oppgaven 2	Nedsatt kvalitet 1	God kvalitet 0	Kommentarfelt:
1 Dynamisk balanse - hoppe				
2 Dynamisk balanse - hinke				
3 Diadokokinese, høyre overekstremitet				
4 Diadokokinese, venstre overekstremitet				
5 Resiprok koordinasjon, overekstremiteter				
6 Tommelfingerbevegelse				
7 Gange				
8 Løft arm				
9 Løft bein				
10 Full strekk				
	Høy tonus 2	Noe forøket tonus 1	Normal tonus 0	
11 Palpasjon av ryggmuskulatur				
	Neds. bev 2	Noe neds bev 1	God bev 0	
12 Passiv bevegelse av høyre hofteledd				
13 Passiv bevegelse av venstre hofteledd				
14 Passiv dorsalfleksjon av høyre fot				
15 Passiv dorsalfleksjon av venstre fot				
	uttalt medb. 2	Mod. Medbev 1	Kun sporadsk 0	
16 Medbevegelse				

Navn: Dato 1. unders. Dato 2. unders. Sumskåre

Kjønn: Evt. diagnose:

Fødselsdato: Testet av: Evt. medisin (angi mg.:) Sumskåre korrigert for manglende deltester

Beregning av 'Sumskåre korrigert for manglende deltester': (Sumskåre / 16) x antall utførte deltester

Fig. 2 shows the MFNU scoring sheet, which allows the test-retest evaluation.

4.8. Interrater assessment on the MFNU

A previous study of rater agreement between physiotherapists, who had received supervision on the use of the MFNU, showed a high to very high rater agreement (Kappa ranging from .67 to 1.00). This was done for sub-tests of an early version of the MFNU (54). In the following we present rater agreement for the 'Total score' of the MFNU version used in paper I and II (17 sub-tests). Furthermore, we present rater agreement for the Total change score.

4.8.1. Interrater agreement on the Total score of MFNU

Participants
Nine municipality physiotherapists, who had limited experience in the use of the MFNU, and who had received no supervision in the use of it, contributed.

Materials
Videos of MFNU assessments of boys with ADHD and normal controls were randomly drawn from a larger sample of videos. Videos of children with ADHD and of children without ADHD were mixed and copied in a random order. A total of ten MFNU assessments were included.

Procedure
Instruction of rating from the MFNU manual and DVD was presented for each sub-test. The physiotherapists then scored the selected video films. Scoring was done individually and the 3-category scoring system was used. Statistical analyses were carried out using SPSS software 16.00. An Intraclass Correlation (ICC) of consistency, using the two-way mixed Cronbach's model, was calculated to measure rater agreement.

Results
An average ICC of .99 (95% confidence interval, 0.98-1.00) was found, $p < .001$.

Conclusion
The 3-category scorings system was found to be highly be reliable.

4.8.2. Interrater agreement on the MFNU Total change score

Participants

Two physiotherapists participated. Both had used the change score system of the MFNU in their clinical work.

Materials

Videos of 24 children who were tested with the MFNU twice a day on two different days were scored.

Procedure

The raters scored videos of MFNU assessments of boys diagnosed with HKD, during baselines and during MPH and Placebo conditions. Two separate displays were used to show test and retest performance. The Total change scores from baseline to MPH condition were used.
The statistical analyses were carried out using SPSS software 16.00. An Intraclass Correlation (ICC) of consistency, using the two-way mixed Cronbach's model, was calculated to measure rater agreement.

Results

An average ICC of 0.99 (95% confidence interval, 0.98, 1.00) was found, $p < .001$

Conclusion

Trained raters, who had previous experience with the change score system of the MFNU showed a high agreement regarding this scoring procedure.

4.9. Aims of the Thesis

The main purpose of the research projects described in this thesis has been to investigate the possible relationship between ADHD symptoms and certain motor functional problems observed in these children. An underlying and important basis was to development the MFNU as a reliable research tool. The development of the MFNU user manual and the accompanying DVD was deemed to be of major importance in this respect. The manual and the DVD are therefore central part of this thesis.

The specific aims of our studies using the MFNU as our research tool were the following:

- To establish to what extent the MFNU is able to discriminate between children with ADHD and children without ADHD. This work is presented in Paper I.

- To investigate the effect of Methylphenidate on motor problems in children with ADHD. This was done in a double blind randomly controlled study presented in Paper II.

- To investigate to what extent motor problems are present in positive responders to MPH on their core behavioural problems of ADHD, compared to non-responders. This retrospective study is presented in Paper III.

- To describe changes in motor function on MPH medication in children who did not fully satisfy the ADHD criteria but were positive medicine responders. These children were diagnosed with 47, XYY syndrome. A case report is presented in Paper IV.

5. Materials and methods

5.1. Participants

5.1.1. The MFNU user manual and the interactive instruction DVD

In the process of finding out whether the information given in the MFNU user manual and in the DVD were understandable for physiotherapists and physicians, more than 150 persons from Troms in the north to Vest-Agder in the south of Norway participated.

In the process of examining whether the information given in the MFNU user manual and the DVD was sufficient to perform a valid MFNU assessment, fourteen physiotherapists from seven municipalities in Norway participated. Approximately 40 children with and without ADHD were assessed.

Five children participated in the videos on the final DVD. Among these were two boys diagnosed with HKD who had been medicated with MPH for several years (age 10 years and 15 years). Three children without ADHD or motor problems also participated, one boy and one girl 5 years old and one girl who was recorded twice (7 and 9 years old). Written informed consent was obtained from the parents. The first author performed the assessments.

5.1.2. Paper I.

The Motor Function Neurological Assessment (MFNU) as an indicator of motor function problems in boys with ADHD

Twenty-five drug-naïve boys, aged 8-12 years and recently diagnosed as HKD F90.0, and 27 controls without ADHD participated. The boys in the ADHD group were all candidates for Methylphenidate evaluation. Diagnostic assessment of the children with HKD was carried out by a physician or a clinical psychologist.

5.1.3. Paper II.

Methylphenidate improves motor functions in children diagnosed with Hyperkinetic Disorder

Participants in this study was the same HKD group as in paper I.

5.1.4. Paper III.

Motor function and Methylphenidate effect in children with ADHD
This was a retrospective study. The group consisted of 73 children diagnosed with ADHD, age 5-17 years (mean 10.75 years, SD 2.57, 36 ≤10 years 37 ≥ 11 years), who had been assessed with parts of the MFNU between 1990 and 1996, and who had been evaluated with regard to effect of central stimulant medication on their core problems of ADHD.

5.1.5. Paper IV

Stimulant medication in 47, XYY syndrome
The study comprised two boys, 12 and 11 years of age referred for assessment of ADHD. Both boys had learning disabilities and social problems.

5.2. Methods

5.2.1. The MFNU user manual and the DVD

The first and the second author of the MFNU manual used qualitative methods when discussing and reflecting on each item of the MFNU (77). Video films and pictures in combination with practical performance were used. Content analysis of written preliminary descriptions of each item was carried out. Revision of the instructions for the sub-tests of a preliminary version of the MFNU was partly based on this.

As part of the ordinary assessment of children with ADHD, the third author of the MFNU manual observed the first author doing assessments during baseline and MPH trials. They discussed the scoring and the test-retest procedure.

Visual methods (78), discussions and reflections were also used in order to assess whether physiotherapists and physicians understood the instructions given in the MFNU user manual and in the text and videos on the DVD. Preliminary manual drafts and video films were used during MFNU lectures. As parts of the lectures all participants performed practical training in the use of MFNU. The user manual and the videos were adjusted according to their feedback and observations

of their testing. Revised instructions and video films were then shown to new physiotherapists; a new adjustment was done and so on.

Written and verbal comments on the comprehensibility of the manual and the instruction DVD were retrieved from physiotherapists who received individual supervision in the method.

There were two training groups consisting of 6 physiotherapists from different municipalities. Group 1 had 4 and group 2 had 6 meetings, each lasting one day, over a period of one year. The preliminary MFNU manual and video films were tested out. The physiotherapists assessed children according to the instructions while a second person taped the assessment. The physiotherapists received feedback on their MFNU assessment from their group. The groups focused on information they felt was lacking in the manual and in the DVD. The user manual and the text and video films on the DVD were adjusted according to the feedback.

5.2.2. Paper I

The study involved two assessments with MFNU, 'Assessment 1' and 'Repeated assessment'. There was an interval of at least 1 day between the assessments. The repeated assessment was performed in order to investigate possible training effects. The subjects were assessed and videotaped individually. The videotapes were later rated by a physiotherapist with no prior experience with the children.

Descriptive statistics were used on data from each sub-test in the ADHD and control group in order to study the percent distribution of the scoring categories (0-1-2) and on the variable 'Total score'. Mann-Whitney U-tests were used to compare the ranked scores of the ADHD- and control group on each of the sub-tests and on the 'Total score'. Chi square tests were used to examining possible effects of age on motor performance. A Cronbach alpha analysis was performed to establish the internal consistency of the total set of sub-tests and the Wilcoxon Signed Rank Test for related samples was used to compare changes in performance on repeated measurements.

5.2.3. Paper II

A double-blind, placebo controlled, cross-over design was applied, using MPH or placebo capsules. A randomization procedure was used for group allocation.

The children were assessed individually with the MFNU twice a day on two different days, with at least one day interval. The first trial each day was baseline and the second was the experimental condition (see Table 4, paper II). The trials were video taped.

A rater with no prior knowledge of any of the children rated the videotapes from each session of each child at a later point in time. The sessions were displayed in a blinded order. Distributions of the scoring categories (0-1-2) and of the change scores for each sub-test and for the TS were obtained from the Baseline, Placebo and MPH conditions. Effects of MPH were analysed using the Wilcoxon Signed-rank test for related samples to compare the performances during Baseline, Placebo and MPH trials on each of the 17 sub-tests and on the TS. Mann Whitney U-tests were used to compare the two groups. Cohen's *d* was used for calculation of the effect size of the TS.

5.2.4. Paper III

The study group (N = 73) was divided into two sub-groups: 'Medicine responders' and 'Non medicine responders'. Independent variables were age in whole years, gender and medicine response. Mann-Whitney U-tests were performed to analyse medicine response depending on age and gender. There were no significant differences between the groups on these variables. Frequency analyses were performed in order to inspect the distribution of scores on the 3 categories of the sub-tests. Mann-Whitney U-tests were used to compare the ranked scores of the groups on each of the 5 sub-tests. A Cronbach alpha analysis was performed to establish the internal consistency of the total set of sub-tests.

5.2.5. Paper IV

In this case study both children underwent a two-day cognitive and neuropsychological test program. They did not fulfil the ADHD-C diagnostic criteria. However, clinical observations led to the conclusion that central stimulant medication was indicated. The children were examined with the MFNU during baseline and retest 90 minutes after administration of 10 mg of MPH.

6. Results

6.1. The MFNU user manual and the DVD

Some sub-tests were removed in the transition from the preliminary version of Modified Function Neurological Assessment to the MFNU user manual. 'Dynamic Balance, jumping on one foot', (ages 5-8) was removed because it requires an open space of 5 metres, which limits the use of the sub-test in an office. The sub-test 'Imitation of match patterns' was removed for practical reasons, because it required suitable chairs and tables for the children. The sub-test 'Throw Ball/Catch Ball was first divided into 'Throw large ball' and 'Catch small ball'. These sub-tests were used in paper I and II, but removed later because the use of balls required a suitable room. These sub-tests gave little additional information regarding the child's difficulties beyond what was identified through the other MFNU sub-tests. The names of some sub-tests were abbreviated and shortened. Separate scores for the left and the right side of the body were obtained for some of the sub-tests.

The MFNU user manual was originally planned to be on a CD. However, during the lectures and supervisions of physiotherapists and physicians, a need emerged for a more detailed user manual in paper and for an interactive DVD. The MFNU user manual has five chapters. The three first chapters are theoretical, chapter IV gives instructions for administration of the MFNU sub-tests and scoring of the sub-tests and chapter V gives instructions for the test - retest procedure and the scoring of this. The DVD contains Power Point presentations which include both text and video illustrations. The DVD is divided into four sections. The first section contains instructions. The following three sections contain video illustrations, spoken instructions and text on

1. how to perform the assessment of the sub-tests,
2. how to score the sub-tests
3. how to score changes in performance.

Videos of MFNU assessments of children with ADHD and children without ADHD or known motor problems are included on the DVD. Illustrations of test-retest procedure and of change due to Methyl-phenidate on the motor performance are also shown.

6.2. Paper I

A high percentage of 'severe problems' was found in most of the sub-tests in the ADHD group. The control group typically presented few, if any severe problems when the 'moderate problems' and 'severe' scores were combined, the ADHD group presented problems within a range of 80 to 96%, (see Table 3, Paper I). The Mann-Whitney U-test showed highly significant differences between the groups on all 17 sub-tests on both assessments. In the ADHD group the strongest differences from the control group were found on the 'Passive movement' and 'Extension' sub-tests. The differences between the ADHD- and the control group were most pronounced for the youngest children (8-10 years). However, significant differences were also obtained between the older children (>= 11 years) except for the sub-test 'Catch ball'. The older ADHD group performed significantly better than the younger group on two sub-tests, 'Reciprocal coordination' and 'Walking'. Mann-Whitney U-tests showed that the ADHD group had significantly more motor problems (higher 'Total score') than the control group. Repeated assessment showed moderate learning effect in the control group, but not in the ADHD group.

6.3. Paper II

There were no significant differences on the 'Total score' between the group receiving MPH the first day and the group receiving MPH the second day when comparing the Baseline, MPH and Placebo sessions. This indicated that the groups could be treated as one (N=24). Table 5 in Paper II shows the relative distribution of scores in the categories 0-2 for the whole group on each sub-test on the Baselines, MPH and placebo condition. The most pronounced improvements with MPH compared to Baseline were observed on the passive movement tests, the extension sub-tests and 'Throw ball'. When the 7 category 'Change score' system was applied, (See Table 7, paper II) a relatively high percentage of the children showed a 'Positive change within the same category' on the 'Dynamic balance – two legs', 'Dynamic balance – one leg', 'Diadochokinesis, left', 'Reciprocal coordination' and 'Walking'. The Wilcoxon Signed-rank test for related samples showed significant improvements on all sub-tests when comparing Baseline 1 with the MPH trial. A Cohen's *d* of 1.27 was found, applying 'Total score' of the MPH and the Baseline 1 trials. According to Cohen (79) this is a large effect size. No significant differences were found between the Baseline 1 and the Placebo trial except for sub-test 10

'Lifting arm' which showed more problems in the Placebo trial. Twenty-three of the boys had a trial period at home and school of MPH response on their ADHD symptoms, after the motor assessments. Among these, twenty-one showed a positive MPH response.

6.4. Paper III

The results showed significantly more motor problems in the MR group compared to the NMR group. The MR group showed moderate or severe motor problems on the 5 sub-tests ranging from 55.4 % ('Reciprocal coordination') to 90.2 % ('Synkinesis'), while the range for the NMR group was 19.0 % ('Reciprocal coordination') to 50.0 % ('Synkinesis') (see Table 2, paper III). A Cronbach Alpha analysis of complete data sets from 62 children on the 5 sub-tests, yielded an alpha of 0.83. This indicated a high internal consistency between the sub-tests, and that the sum of the set of sub-tests ('Total score') could be used as a continuous scale. One-Sample Kolmogorov-Smirnov test yielded a significant result suggesting violation of the assumption of a normal distribution. The Mann-Whitney U-tests showed that all the 5 sub-tests and the 'Total Score' discriminated significantly between the groups. The MR-group obtained a significantly higher median score than the NMR-group on all the sub-tests (see Table 4, Paper III). The sub-tests 'Synkinesis' and 'Dynamic balance' discriminated best between the groups. 'Walking' was the least discriminating sub-test. Mann Whitney U-tests showed no significant differences between the younger and the older children in the MR-group or in the NMR-group on any of the sub-tests. However, when data from the whole group were compared, significant differences for the sub-test 'Reciprocal coordination', 'Walking' and 'Total score' were found. Chi-square tests showed no differences between gender on the 'Total score' or any of the sub-tests

6.5. Paper IV

Both children demonstrated severe problems on all the sub-tests of the MFNU on the baseline trial and improvements when medicated with MPH. The results of the MFNU baseline scores and the change scores from baseline to the MPH trial are shown in Table I in Paper IV. Palpation of the m. Erector spinae, m. trapezius and m. Latissimus dorsi revealed muscles with hyper- and hypotonic areas, which differed from what is usually found in children with ADHD. Based on prior experience, this finding together with the height (both were above

97.5% height for their age) and tremor indicated chromosome analysis and 47,XYY syndrome was diagnosed. Both boys showed positive effect of MPH regarding attention and social problems.

7. Discussion and limitations

7.1 The MFNU as a research instrument

The central aim of the research projects was to investigate possible relationships between ADHD symptoms and certain motor problems observed in children with the ADHD-diagnosis. These observations were made over many years in clinical and educational settings. The MFNU was constructed and developed as part of this research. The reliability and usefulness of this instrument as a clinical assessment tool had been demonstrated through many years of practice with hundreds of children at the Birkelid Resource Centre prior to the start of the research. However, the MFNU was not originally constructed as a research tool. Since the usefulness of the instrument in this respect is of crucial importance to the validity of our research findings, much effort was put into development of a user manual with precise instructions for test administration on each subtest, together with rules for inter-pretation and scoring.

In clinical settings the 3-category scoring system had proved to give a fair compromise between reliability considerations and the need for precision. The scoring system is easy to administer, and yields a high agreement among physiotherapists. Although the MFNU seems robust and stable as a clinical instrument, the rank order 3-category system has certain weaknesses when applied in research, mainly because of its inherent limitations where statistical analysis is concerned (ordinal scale). A more differentiating scaling system would have allowed for more sophisticated statistical analyses. Such analyses might in turn lead to scoring categories suitable for differentiations between clinical groups.

While the weaknesses of the scoring system prohibit advanced statistical analysis, the results presented in Paper I-III prove such limitation to be irrelevant as to the determination of differences between groups. The results of the data analyses gave strong support to our hypotheses.

In a clinical situation the MFNU is scored by the therapist who is assessing the child. To avoid rater bias video scoring by an independent rater was used in Study I and II. Observation and scoring from

videotape is different from examining a child in a clinical setting and introduces the possibility of differences in scoring. Video scoring limits the possibility of evaluating subtle observations, in particular muscular consistency. Important clinical information is lost when the scoring is based on a video recording. Nevertheless, the differences between the compared datasets in study I and II were pronounced and indicated that the limitations of video scoring did not contaminate the results seriously.

7.2. Paper I.

The Motor Function Neurological Assessment (MFNU) as an indicator of motor function problems in boys with ADHD.

We wanted to establish to what extent the sub-tests of the MFNU discriminated between children with ADHD-C/HKD and children without ADHD symptoms. Highly significant differences were found between the groups on all 17 sub-tests. Re-testing 1 day or more after the first test showed no training effect in the ADHD group. A high percentage of 'severe problems' in most of the sub-tests was found in the ADHD group. The control group typically presented few, if any severe problems. When the 'moderate problems' and 'severe problems' scores were combined, the ADHD group presented problems in the range of 80 to 96%. This result reveals that the MFNU not only discriminates well between children with the HKD/ADHD-C diagnosis and normal controls. It also suggests that motor problems may play a more integrated part in the ADHD condition than earlier assumed. Another important finding was that the strongest differences from the control group were found on the 'Passive movement' and 'Extension' sub-tests which contradict the assumption that motor problems in ADHD are due to distraction and impulsivity.

The fact that the MFNU discriminates well between a strictly defined HKD/ADHD-C group and normal controls, raises a number of questions concerning the occurrence of similar problems in the broader ADHD population and in other clinical groups. The results of the retrospective study (Paper III), investigating a broad ADHD sample of both sexes, suggest that motor problems (as measured by the MFNU) are less apparent in the ADHD-predominantly Inattentive and ADHD-predominantly Hyperactive subgroups. It is also probable that many children with ADHD have a comorbid DCD disorder, which in many cases would result in high scores on many of the MFNU subtests. This

makes it difficult to decide to what extent the "MFNU-problems" are integral parts of the ADHD syndrome, or – as assumed by most researchers today – that motor problems seen in ADHD are comorbid to the condition.

Methodological issues in Study I

A possible threat to the validity of our findings is related to the non-blinded design used in the first study (Paper I), allowing potential rater bias. The ADHD group and the control group were assessed at different locations. Knowledge of the group adherence of each child, and possibly also the fact that the two groups were assessed at different places may have contributed to biases in measurement. However, a more blinded design would not have eliminated rater bias because the experienced rater would easily have guessed the group-membership of the children with ADHD from their restless and impulsive behaviour. While scoring bias due to prejudiced rater expectations may have contributed to a falsely high difference between the ADHD- and control group, the very significant differences shown in our study rule out the possibility that biased rating alone could explain the findings. The measurement design based on videotapes as the source of rating makes it highly unlikely that the differences observed in motor performance between the groups was the result of such measurement errors. The high interrater reliability of the MFNU further strengthens this conclusion.

7.3. Paper II.

Methylphenidate improves motor functions in children diagnosed with Hyperkinetic Disorder.

The results presented in Paper II showed that medication with a single dose of MPH yielded a significant improvement on all the MFNU sub-tests compared to baseline and placebo conditions. The passive movement tests, the extension sub-tests and 'Throw ball' (revealing high muscle tone in muscles of the trunk, shoulders and hips) showed the most pronounced improvements. A high percentage of the children showed improved movement when medicated with MPH on the motor inhibition sub-tests. The positive MPH effect on motor functions and the reoccurrence of the problems when the MPH was metabolized are very similar to what is seen in the behavioural symptoms of ADHD when medication is withdrawn.

Taylor et al. (80) studied the relationship between ADHD symptoms as defined by the DSM-III and ICD-9 and response to MPH. A positive response to MPH was predicted by higher levels of inattentive and restless behaviour, impaired performance on tests of attention and *clumsiness*, among others – but not by the diagnostic criteria of ADHD in themselves. Zeiner et al. (68) found that stimulant medication was associated with improvement on motor steadiness. These studies lend further support to our findings.

Methodological issues in Paper II

The study was double blinded and the results should therefore not be vulnerable to rater bias. A potentially problematic part of the design of this study concerns the use of one scoring sheet for all observations. Thereby the raters had access to prior scoring marks. It is quite possible that the results would have been weaker if the raters had been blinded to prior ratings. However, the rating procedure, which is the standard way of evaluating test-retest performance with the MFNU, was chosen to make an evaluation of changes in performance both *across* categories and *within* the same category possible. The use of a blinded 3-category rating of each trial would probably have missed out many of the clinically important differences. The fact that our design applying the dual screen setup and single sheet scoring has proven reliable in interrater-reliability analyses makes it improbable that rater bias influenced the results in any important way.

7.4. Paper III

Motor function and Methylphenidate effect in children with ADHD.

The study presented in Paper III investigated to what extent motor problems are present in clinically positive responders to MPH, compared to nonresponders. Significantly more motor problems were found in subjects with a positive MPH response than in those who did not respond to medication. The results of our study are in accordance with the research referred, where motor clumsiness (80) was reported as a predictor of MPH response, together with inattention and restlessness. The results seem to point out a functional link between the brain processes involved in the motor problems and the processes regulating the behavioural symptoms of ADHD.

Study I and II were performed on boys only, which restricts the possibility of generalization. The sample of this retrospective study consisted of both genders, although the number of girls was relatively low. No differences were found in performance that could be attributed to gender. This was also the case with age differences. This suggests that the results obtained with the sample of boys in Study I and II is representative of the ADHD population at large.

Methodological issues in Paper III

The study was retrospective and based on a sample of children accumulated over 6-7 years. The strength of this design was that the rating of MFNU was done independently and prior to the diagnosis and assessment of central stimulants. The strong relationship shown between motor problems and MPH response could therefore not be due to rater bias. The results were based on several evaluations of medicine response at the Resource Centre. The assessment and diagnostic procedures were thorough and based on a multi-disciplinary consensus, thus leaving small room for misdiagnosis and mistakes in the evaluation of MPH effect during the observation period. However the retrospective design of the study prohibited access to information about the prolonged effects of medication after the evaluation period. Possible long term negative responses in some of the subjects have therefore not been accounted for in the study. Another weakness is the lack of full scale MFNU at the time of assessment. The retrospective data were accumulated from an early period of the development of MFNU (1990-1996) when the test only included a limited number of sub-tests compared to the published version (mostly motor inhibition tests, and no sub-tests assessing muscle tone). These limitations imply that the results should be interpreted with caution.

7.5. Paper IV

Stimulant medication in 47,XYY syndrome.

This paper was included in the thesis to demonstrate that MPH response may be less associated with the behavioural symptoms of ADHD than with the presence of the specific motor problems assessed with the MFNU. The paper presents case studies of two boys diagnosed as 47,XYY. Both boys showed improved motor and behavioural function when medicated with MPH. On the basis of this and other studies showing positive MPH response in individuals with few ADHD symptoms, one might speculate that the MPH response is not

necessarily targeting the higher order neural processes of executive functions. Perhaps lower order processes associated with motor control, motor inhibition and arousal, explains the improvements with MPH on motor control, body stability and muscle tone documented in Study II.

The high percentage of subjects with motor problems and a positive MPH response shown in Study III may further support this suggestion. Correspondingly, our findings that ADHD subjects with little motor problems displayed a weak or negative MPH response may indicate a subgroup of ADHD with a different neurological status than the positive MPH responders.

7.6. General implications of our findings

Throughout our research projects the major question was: What is the role of motor problems in ADHD and why do these motor problems seem as responsive to central stimulant treatment as the behavioural symptoms of ADHD? Does the MPH response on motor problems revealed by the MFNU point to a common neurofunctional core problem, present only in MPH responders, and may the MFNU serve as a marker for this condition? Even if there may be positive MPH responders with few or no motor problem on the MFNU, as seen in Study II, the connection between motor problems and MPH response is so marked that this question should be further investigated.

We have discussed whether the positive stimulant responders may have certain neurofunctional problems in common that are different from those seen in non-responders. Our findings may seem to support this notion. Much criticism has been raised against the DSM-IV definition of ADHD for the inclusion of clinical groups that may have different problems as the basis of their overt behaviour (13, 81). Many researchers have questioned the validity of the diagnosis, due to the use of very broad inclusion criteria, and to the reliance on behavioural criteria only (82). The lack of neurofunctional markers and other somatic indicators of the condition makes the evaluation of research results on ADHD very difficult (10). This is particularly relevant where research on stimulant effects on ADHD is concerned. About 20-30 % of individuals with the DSM-IV ADHD diagnosis display a lack of response or worsening of behaviour in response to stimulants (83). As stated earlier the ICD-10 is more restrictive than the DSM-IV.

7.6.1. The functional links between motor problems and ADHD

The results of our studies point to the possibility that the presence of certain motor deficits associated with inhibition and muscular tone may be a key to a better understanding of the differences in stimulant response within the ADHD-group. They may subsequently lead to a better functional understanding of the condition. The possible nature of the relationship between the motor problems and the attention deficits /behavioural inhibition problems of ADHD is still unclear. We have suggested some neurological links and in particular the dopamine regulated fronto-striatal system (23). MPH is known to influence neuromodulators like dopamine and nor-epinephrine. These are neuro-modulators that affect both the motor system and vigilance (41). The motor inhibition problem may point to a cerebellar dysfunction (84) and support the theory of a dysfunction in the cerebello-thalamo-prefrontal circuit (28). A link through the parallel reticular regulation of arousal and body stabilization has been suggested. Reticulospinal tracts convey nerve signals to muscles in the torso, shoulders and hips, that maintain change of posture, equilibrium and balance (85). Our research has shown that children with ADHD have a high tone in muscles of these body parts and that the tone is normalized with a single dose of MPH.

7.6.2. Practical implications

The MFNU project started out with the practical goal of developing a test that would reveal problems seen in ADHD subjects in an easy way. Such problems were often ignored or misinterpreted by parents and teachers – and by themselves. By pointing out their interpretation of the behaviour as disobedience and laziness striking changes could be observed in the behaviour of the adults – and eventually in the child. With the introduction of MPH in the MFNU testing situation this change was even more striking.

Apart from use in educational settings, the MFNU may, as a result of the documentation provided by our research projects, serve as a valuable tool in the differential diagnosis of ADHD and as a supplemental predictor of positive of MPH response.

So far we have found no successful method to access and train the specific problems revealed by the MFNU in ADHD, perhaps with an exception for some of the problems with muscular tone and stability. Such training has been successful in the treatment of encopresis (75).

The scientific documentation of specific motor training is scarce, and we would like to see future research in the field. In contrast typical DCD problems were often responsive to intervention (35, 86). Further controlled studies are needed to get a more precise answer to whether the motor problems in ADHD are of a different functional nature than those of DCD

8. Conclusions and implications

The MFNU has been shown to be a sensitive instrument in the assessment of motor inhibition and high muscle tone in trunk, shoulders, hips and legs in boys with ADHD-C/HKD. Interrater agreement was presented in paragraph 4.8 in the Introduction. However future studies of rater agreement among physiotherapists are needed.

The results of the research presented in this thesis support our clinical observations regarding specific motor problems in children with ADHD. We found such problems both in the diagnostic group in general and in children with ADHD who respond positively to central stimulant medicine in particular. The results also demonstrate that the motor problems identified by the MFNU are present in a very high percentage of children with ADHD. The results support our suggestion that there may be a close relationship between the motor problems measured by the MFNU and the neurofunctional basis of ADHD. This relationship is supported by the finding that administration of a single dose of MPH in boys diagnosed as ADHD-C yielded a significant improvement of the motor problems. There was a corresponding weaning effect after the metabolisation of the MPH which is very similar to what is seen in the behavioural symptoms of the syndrome. Our results show that the presence of a high 'Total score' on the MFNU increases the probability of a positive MPH response, and that a low score decreases this probability.

Future controlled replication studies with clearly defined diagnostic groups are needed to determine the exact role of motor problems in MPH response, and their functional relation to the core ADHD symptoms. There are children with few or no motor problems on the MFNU who respond to MPH on their core problems of ADHD, as seen in Paper II. It is important to search for the characteristics of this group.

It is premature to conclude that the MFNU can be used as a marker in the diagnosis of ADHD. Some individuals who satisfied the ADHD criteria showed few or no motor problems on the MFNU. Other clinical groups may also demonstrate high MFNU-scores without satisfying the ADHD criteria. However, our results indicate that the MFNU can be used as a predictor of a positive clinical MPH response. This result, together with the corresponding finding that a low MFNU

score is associated with a modest MPH response, may contribute to a better theoretical understanding of the core neurofunctional processes of ADHD. It may also identify different subgroups of ADHD. The MFNU served as an important supplement in the evaluation of MPH treatment in the children who turned out to satisfy the criteria for 47, XYY diagnosis. It is reasonable to assume that the MFNU may contribute to a different view on the role and possibilities of stimulant medication in other clinical conditions than ADHD. Future studies are needed to confirm our findings and to investigate to what extent the results can be replicated in girls and in adolescents and adults persons with ADHD.

Further research on the effect of specific training of muscular function in children with ADHD, like training of the deep stabilizing muscles of the column and other physiotherapy treatment procedures, is needed. The implications of our findings on educational practice also call for further elaboration and research.

The MFNU is still in need of further validation research, particularly regarding the use in diagnostic assessment.

9. References

1. Lier L, Michelsen N. Fumlere og tumlere: nogle studier om kluntede skolebørn. Universitet K, editor. København: FADL's Forlag; 1978.
2. Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery : theory and clinical interpretation. 2nd ed. Tucson, Ariz.: Neuropsychology Press; 1993.
3. Pitcher TM, Piek JP, Hay DA. Fine and gross motor ability in males with ADHD. Dev Med Child Neurol. 2003 Aug;45(8):525-35.
4. Kadesjö B, Gillberg C. The Comorbidity of ADHD in the General Population of Swedish School-age Children. J Child Psychol Psychiatry 2001;42:487-92.
5. Stray LL, Iversen S, Stray T, Ellertsen B, Ruud A. MFNU - Motorisk Funksjonsnevrologisk Undersøkelse Brukermanual. Stavanger: Universitetet i Stavanger; 2006.
6. Sagvolden T, Archer T. Attention deficit disorder : clinical and basic research. Hillsdale, N.J.: L. Erlbaum Associates; 1989.
7. Barkley RA. The Executive Functions and ADHD. In: Lombroso PJ, editor. Genetics of Childhood Disorders. New Haven: American Academy of Child and Adolescent Psychiatry Volume 2000. p. 1064-8
8. WHO. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.
9. APA. American Psychiatric Association, Diagnostic and statistical manual of mental disorders 4th ed. Washington, DC: Author; 1994.
10. Swanson JM, Sergeant JA, Taylor E, Sonuga-Barke EJ, Jensen PS, Cantwell DP. Attention-deficit hyperactivity disorder and hyperkinetic disorder. Lancet. 1998 Feb 7;351(9100):429-33.
11. APA. Disorders Usually First Diagnosed In Infancy, Childhood, or Adolescence. 2009 [updated 2009; cited]; Available from: http://www.psych.org/MainMenu/Research/DSMIV/DSMIVTR/DSMIVvsDSMIVTR/SummaryofTextChangesInDSMIVTR/DisordersUsuallyFirstDiagnosedInInfancyChildhoodorAdolescence.aspx.
12. Tasman A, First MB. DSM-IV-TR mental disorders: diagnosis, etiology, and treatment. Chichester: John Wiley; 2004.

13. Barkley RA. Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. New York: Guilford Press; 1998.
14. Biederman J, Mick E, Faraone SV, Braaten E, Doyle A, Spencer T, et al. Influence of Gender on Attention Deficit Hyperactivity Disorder in Children Referred to a Psychiatric Clinic. Am J Psychiatry. 2002 January 1, 2002;159(1):36-42.
15. Barkley RA. Attention-deficit hyperactivity disorder : a handbook for diagnosis and treatment. 2nd ed. New York: Guilford Press; 1998.
16. Castellanos FX, Giedd JN, Marsh WL, Hamburger SD, Vaituzis AC, Dickstein DP, et al. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Arch Gen Psychiatry. 1996;53(7):607-16.
17. Castellanos FX, Swanson J. Biological underpinnings of ADHD. In: Sandberg S, editor. Hyperactivity and Attention-Deficit Disorders. 2nd ed. Cambridge: Cambridge University Press; 2002.
18. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997;121(1):65-94.
19. Overtoom CCE, Kenemans JL, Verbaten MN, Kemner C, van der Molen MW, van Engeland H, et al. Inhibition in children with attention-deficit/hyperactivity disorder: a psychophysiological study of the stop task. Biol Psychiatry. 2002;51(8):668-76.
20. Pliszka SR, Liotti M, Woldorff MG. Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. Biol Psychiatry. 2000;48(3):238-46.
21. Sergeant J. The cognitive-energetic model: an empirical approach to attention-deficit hyperactivity disorder. Neurosci Biobehav Rev. 2000 Jan;24(1):7-12.
22. Johansen EB, Sagvolden T. Slower extinction of responses maintained by intra-cranial self-stimulation (ICSS) in an animal model of attention-deficit/hyperactivity disorder (ADHD). Behavioural Brain Research. 2005;162:22–31.
23. Sagvolden T, Johansen E, Aase H, Russell V. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. Behav Brain Sci. 2005;28(3):397-419.

24. Rubia K, Taylor E, Smith AB, Oksannen H, Overmeyer S, Newman S. Neuropsychological analyses of impulsiveness in childhood hyperactivity. Br J Psychiatry 2001;179:138-43.
25. Rubia K, Oosterlaan J, Sergeant J, Brandeis D, Leeuwen T. Inhibitory dysfunction in hyperactive boys. Behav Brain Res. 1998;94:25–32.
26. Castellanos FX. Toward a pathophysiology of attention-deficit/ hyperactivity disorder Clin Pediatr. 1997;36:381-93.
27. Zang Y-F, He Y, Zhu C-Z, Cao Q-J, Sui M-Q, Liang M, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev. 2007;29(2):83-91.
28. Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, et al. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. Neurology. 1998 Apr;50(4):1087-93.
29. Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T, et al. Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2001 March 1, 2001;58(3):289-95.
30. Bradshaw JL. Developmental disorders of the frontostriatal system: neuropsychological, neuropsychiatric, and evolutionary perspectives. Hove: Psychological Press; 2001.
31. Swanson J, McBurnett K, Wigal T. Effect of stimulant medication on hyperactive children: a review of reviews. Exceptional Children. 1993;60:154-62.
32. Wilens T, Biederman J. The stimulants. Psychiatr Clin North Am. 1992;15:191–222.
33. Swanson J, Volkow ND. Stimulant drugs and ADHD: Basic and clinical neuroscience. In: Solanto MV, Arnsten AFT, Castellanos FX, editors. New York: Oxford Univ. Press; 2001. p. 259–82.
34. Smythies JR. The Neuromodulators. International review of neurobiology. [Review]. 2005;64:1-271.
35. Iversen S. Children with developmental problems and disorders: selected aspects of motor and multidisciplinary assessment and intervention [Dr. philos thesis]. Bergen: University of Bergen; 2006.
36. Tantorski EP. Functional Neuroanatomy, PT 342-343 Neuroanatomy I and II. Hamden CT: Academic Technology Quinnipiac University; 2007 [cited 2009 28.aug]. Available from: http://faculty.quinnipiac.edu/health/tantorski/index.html.
37. Carlson NR. Physiology of behavior. 9 ed. Boston: Pearson Allyn & Bacon; 2007.

38. Leiner H, Leiner A, RS D. Reappraising the cerebellum: what does the hindbrain contribute to the forebrain? Behav Neurosci. [Review]. 1989;103(5):998-1008.
39. Ivry R. Cerebellar timing systems. Int Rev Neurobiol. 1997;41:555–73.
40. Mosby's Medical Dictionary. 8th ed.: Elsevier; 2009.
41. Brodal P. Sentralnervesystemet. 3 ed. Oslo: Universitetsforlaget; 2001.
42. Brodal P, Brodal A. Sentralnervesystemet: bygning og funksjon. Oslo: TANO; 1990.
43. Takakusaki K, Kohyamaa J, Matsuyamab K. Medullary reticulospinal tract mediating a generalized motor inhibition in cats: iii. functional organization of spinal interneurons in the lower lumbar segments Neuroscience 2003;121(3):731-46.
44. Sergeant JA, Piek JP, Oosterlaan J. ADHD and DCD: A relationship in need of research. Hum Mov Sci. 2006;25(1):76-89.
45. Kadesjö B, Gillberg C. Attention deficits and clumsiness in Swedish 7-year-old children. Dev Med Child Neurol. 1998 Dec;40(12):796-804.
46. Bruininks RH. Bruininks-Oseretski test of motor Proficiency: Examiner's manual. Circle Pines, MN: American Guidance Service; 1978.
47. Henderson SE, Sugden DA. Movement assessment battery for children. London, UK The Psychological Corporation; 1992.
48. Wilson BN, Kaplan BJ, Crawford SG, Campbell A, Dewey D. Reliability and validity of a parent questionnaire on childhood motor skills. The American Journal of Occupational Therapy. 2000;54:484–93.
49. Dewey D, Cantell M, Crawford SG. Motor and gestural performance in children with autism spectrum disorders, developmental coordination disorder, and/or attention deficit hyperactivity disorder. Journal of the International Neuropsychological Society. 2007;13:246-56.
50. Kaplan BJ, Wilson BN, Dewey D, Crawford SG. DCD may not be a discrete disorder. Hum Mov Sci. 1998 August;17(4-5):471-90.
51. Reitan RM, Davidson LM, editors. Chlinical Neuropsychology. Current status and applications. Washington DC: V.H.Winston; 1974.
52. Domellöf E. Development of functional asymmetries in young infants: A sensory-motor approach [Doctoral dissertation]. Umeå, Sweden: Umeå University; 2006.

53. Crawford SG, Wilson BN, Dewey D. Identifying developmental coordination disorder: Consistency between tests. Physical and Occupational Therapy in Pediatrics. 2001;20:29–50.
54. Stray LL. Motorikk hos barn med ADHD: en retrospektiv studie av motoriske vansker hos barn med ADHD basert på modifisert funksjonsnevrologisk undersøkelse (MFNU). Bergen: Universitetet i Bergen; 2001.
55. Piek JP, Pitcher TM, Hay DA. Motor coordination and kinaesthesis in boys with attention deficit-hyperactivity disorder. Dev Med Child Neurol. 1999 Mar;41(3):159-65.
56. Tseng MH, Henderson A, Chow SMK, Yao G. Relationship between motor proficiency, attention, impulse, and activity in children with ADHD. Dev Med Child Neurol. 2004;46(6):381.
57. Denckla MB, Rudel RG. Anomalies of motor development in hyperactive boys. Ann Neurol 1978;3(3):231-3.
58. Meyer A, Sagvolden T. Fine motor skills in South African children with symptoms of ADHD: influence of subtype, gender, age, and hand dominance. Behav Brain Funct. 2006;2(1):33.
59. Harvey WJ, Reid G. Attention deficit/hyperactivity disorder: a review of research on movement skill performance of and physical fitness. Adapt Phys Activ Q. 2003;20:1-25.
60. Racine MB, Majnemer A, Shevell M, Snider L. Handwriting Performance in Children With Attention Deficit Hyperactivity Disorder (ADHD). J Child Neurol. 2008 April 1, 2008;23(4):399-406.
61. Raberger T, Wimmer H. On the automaticity/cerebellar deficit hypothesis of dyslexia: balancing and continuous rapid naming in dyslexic and ADHD children. Neuropsychologia. 2003;41(11):1493-7.
62. Kroes M, Kessels AGH, Kalff AC, Feron FJM, Vissers YLJ, PhD JJ, et al. Quality of movement as predictor of ADHD: results from a prospective population study in 5- and 6-year-old children. Dev Med Child Neurol. 2002;44:753-60.
63. Miyahara M, Piek JP, Barrett N. Accuracy of drawing in a dual-task and resistance-to-distraction study: motor or attention deficit? Hum Mov Sci. 2006 Feb;25(1):100-9.
64. Yan JH, Thomas JR. Arm movement control: Differences between children with and without attention deficit hyperactivity disorder. Res Q Exerc Sport. 2002;73:10-8.
65. Eliasson A-C, Rösblad B, Forssberg H. Disturbances in programming goal-directed arm movements in children with ADHD. Dev Med Child Neurol 2004;46:19–27.

66. Kalff A, de Sonneville L, Hurks P, Hendriksen J, Kroes M, Feron F, et al. Low- and high-level controlled processing in executive motor control tasks in 5-6-year-old children at risk of ADHD. J Child Psychol Psychiatry. [Comparative Study
Research Support, Non-U.S. Gov't]. 2003;44(7):1049-57.
67. Harvey WJ, Reid G, Grizenko N, Mbekou V, Ter-Stepanian M, Joober R. Fundamental Movement Skills and Children with Attention-Deficit Hyperactivity Disorder: Peer Comparisons and Stimulant Effects. J Abnorm Child Psychol. 2007;35:871-82
68. Zeiner P, Bryhn G, Bjercke C, Truyen K, Strand G. Response to methylphenidate in boys with attention-deficit hyperactivity disorder. Acta Paediatrica. 1999;88(3):298-303.
69. Lerer RJ, Lerer MP, Artner J. The effects of methylphenidate on the handwriting of children with minimal brain dysfunction. J Pediatr. [Clinical Trial, Journal Article, Randomized Controlled Trial]. 1977;91:127-32.
70. Flapper BCT, Houwen S, Schoemaker M, M. Fine motor skills and effects of methylphenidate in children with attention-deficit-hyperactivity disorder and developmental coordination disorder. Dev Med Child Neurol. 2006;48(3):165.
71. Rubia K, Noorloos J, Smith A, Gunning B, Sergeant J. Motor timing deficits in community and clinical boys with hyperactive behavior: the effect of methylphenidate on motor timing. J Abnorm Child Psychol. 2003 Jun;31(3):301-13.
72. Bedard A-C, Ickowicz A, Logan G, Hogg-Johnson S, Schachar R, Tannock. Selective Inhibition in children with Attention-Deficit Hyperactivity Disorder off and on Stimulant Maediscation. Journal of Abnormal Child Psychology. 2003;31:315-27.
73. O'Driscoll GA, Dépatie L, Holahan A-LV, Savion-Lemieux T, Barr RG, Jolicoeur C, et al. Executive Functions and Methylphenidate Response in Subtypes of Attention-Deficit/Hyperactivity Disorder. Biol Psychiatry. 2005.
74. Cailliet R. Low back pain syndrome. Philadelphia: Davis; 1968.
75. Stray LL. Noen encopreseproblemer kan behandles med fysioterapi. Barnestafetten. 2003;40:16-9.
76. Rasmussen P, Gillberg C. Perceptual, motor and attentional deficits in seven-year-old children. Paediatric aspects. Acta paediatrica Scandinavica. 1983;72(1):125-30.
77. Kvale S. Interviews: Learning the craft of qualitative research interviewing. 2nd ed. London: SAGE Publications Inc.; 2008.

78. Paule MG, Rowlandb AS, Fergusona SA, Chelonisc JJ, Tannockd R, Swansone JM, et al. Attention deficit/hyperactivity disorder: characteristics, interventions and models Neurotoxicology and Teratology 2000 September-October 22(5): 631-51.
79. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9.
80. Taylor E, Schachar R, Thorley G, Wieselberg H, Everitt B, Rutter M. Which boys respond to stimulant medication? A controlled trial of methylphenidate in boys with disruptive behaviour. Psychol Med. 1987;17(1):121-43.
81. Ellertsen B, Johnsen IB. Hyperactivity. In: Ayers S, Baum A, McManus C, Newman S, Wallston S, Wallston K, et al., editors. Cambridge handbook of psychology, health and medicine. Cambridge: Cambridge University Press; 2007. p. 740-2.
82. Castellanos FX, Tannock R. Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. Nat Rev Neurosci. 2002;8(3):617-28.
83. DuPaul GJ, Barkley RA, Conner DE. Stimulants. In: Barkley RA, editor. Attention-deficit hyperactivity disorder: a handbook for diagnosis and treatment. New York: Guilford Press; 1998.
84. Tracy JI, Faro SS, Mohammed FB, Pinus AB, Madi SM, Laskas JW. Cerebellar mediation of the complexity of bimanual compared to unimanual movements. Neurology. 2001;57(10):1862-9.
85. Greenfield S. The Human mind explained: an owner's guide to the mysteries of the mind. New York: Henry Holt; 1996.
86. Pless M, Carlsson M. Effects of Motor Skill Intervention on Developmental Coordination Disorder: A Meta-Analysis Adapted Physical Activity Quarterly. 2000;17(4):381-401.

10. The MFNU manual and PAPERS I-IV

The MFNU manual is enclosed as a separate item.

Paper I

Paper II

Paper III

Paper IV