Table of Contents

Summary

We use our hands and fingers every day to engage with our surroundings. Development of fine motor functions therefore represents a cornerstone of human motor development. This is likely related to maturation and refinement of the central nervous system (CNS), but we know very little about these processes and how they relate to motor control. The aim of this thesis is to investigate how the CNS supports dexterous motor functions, and what happens in the CNS when we become more proficient, e.g. as we progress from childhood to adulthood, and when we engage in motor practice. To this end, I recorded electroencephalographic (EEG) and electromyographic (EMG) activity in a large cross section of children, adolescents and adults (age range 8-30y) while they performed and practiced visuo-motor tasks that required precise control of force between their index finger and thumb. Analyses of EEG and EMG signals were used to quantify the interactions between the activity of cortical brain areas and of the intrinsic hand muscles to reveal functional and effective connectivity at different levels of the CNS.

Manuscript I shows that fine motor performance improves with age. It further shows that oscillatory activity recorded from the cortex and muscle is more synchronized in adults compared to children. This suggests that adults display greater levels of coupling between the cortex and the hand muscles during dexterous motor tasks. **Manuscript II** investigates the coupling between different areas of cortex involved in motor control, and found that some patterns of connectivity were present and functionally relevant to performance already by 8 years of age, whereas others became functionally effective starting from late adolescence. **Manuscript III** investigates age-related differences in the ability to acquire and retain a new motor skill involving dexterous control of the fingers. The results shows that adolescents and adults quickly improve their motor performance during practice. Children also displays improved motor performance during practice, but to a smaller extent than adolescents and adults. On the other hand, children were the only ones who displayed improved performance when they returned 24 hours after motor practice. **Manuscript IV** investigates differences in practice-induced changes in cortical and corticospinal connectivity. The results show that older adolescents and adults display pronounced upregulations in coupling after practice, while this is not the case for children or younger adolescents. Taken together with the results from Manuscript III, these findings suggest that the mechanisms used and the ability to acquire and retain new motor skills differ in children, adolescents and adults.

The results of the thesis help us understand how the CNS controls fine movements and how this is different between children, adolescents and adults. They also provide a better understanding of how the CNS responds to motor practice and how these adaptations are influenced by age. This may improve our understanding of the mechanisms underlying human motor control and skill learning throughout development. The results are not only interesting from a basic science perspective. They also contribute with information that may ultimately aid in the development and refinement of interventions that can be used to improve motor functions and skill learning for individuals with neuro(typical) development and individual with movement disorders.

Dansk resumé (Danish summary)

Vi bruger vores hænder og fingre på daglig basis til at interagere med vores omverden. Udviklingen af håndens motoriske funktioner udgør derfor en af de vigtigste milesten i børns motoriske udvikling. Forbedring af vores finmotoriske funktioner med alderen er formentlig relateret til modning af centralnervesystemet, men vi ved meget lidt om disse modningsprocesser, og hvordan de relaterer sig til vores motoriske kontrol. Hovedformålet med denne PhD afhandling er derfor at undersøge hvordan nervesystemet styrer finmotoriske bevægelser, og hvad der sker i nervesystemet, når vi bliver dygtigere til netop dette fra barnsben til voksenlivet og med motorisk træning. Til dette formål opsamlede jeg målinger af hjernens og håndmusklers aktivitet ved hjælp af elektroencefalografi (EEG) og elektromyografi (EMG) i et stort tværsnit af børn, unge og voksne (mellem 8-30 år), mens de udførte og øvede sig i visuo-motoriske opgave, der krævede præcis styring af kraft mellem deres pege- og tommelfinger. Ved hjælp af analyser af EEG og EMG signalerne blev interaktioner mellem aktiviteten fra forskellige hjerneområder og håndmusklerne beregnet, og brugt som mål for den funktionelle og effektive kommunikation i nervesystemet.

Artikel I viser at den finmotoriske præstation bliver bedre med alderen. Resultaterne viser yderligere at koblingen mellem hjernens og fingermuskulaturens aktivitet er stærkere i voksne end i 8-10 årige børn. Disse resultater indikerer at hjernens og musklens aktivitet under en finmotorisk opgave er mere synkront koordineret for voksne sammenlignet med børn. **Artikel II** undersøger koblingen mellem forskellige områder af hjernens cortex involveret i motorisk kontrol og viser at visse corticale kommunikationsmønstre er tilgængelige og relateret til motorisk færdighedsniveau allerede fra 8-års alderen, hvorimod andre først er til stede og effektive senere i udviklingen. **Artikel III** undersøger aldersrelaterede forskelle i evnen til at tilegne sig og fastholde en ny fingerfærdighed. Resultaterne viser at unge og voksne hurtigt bliver meget dygtigere, mens de trænerfærdigheden. Børn bliver også bedre mens de træner, men i mindre grad end unge og voksne. Til gengæld bliver børnene som de eneste bedre efter træningen er overstået. **Artikel IV** undersøger aldersrelaterede forskelle i kommunikationen mellem hjernens og rygmarvens netværk som følge af motorisk træning. Resultaterne viser at unge i den sene del af puberteten og voksne udviser markante ændringer i koblingen mellem områder af hjernens cortex og rygmarven efter træning, mens dette ikke er tilfældet for børn eller unge i den tidlige del af puberteten. Sammenholdt med resultaterne fra artikel III tyder disse fund på, at de mekanismer, der ligger til grund for tilegnelse og fastholdelse af nye motoriske færdigheder, er forskellige i børn, unge og voksne.

Fundene i afhandlingen bidrager til en øget forståelse af centralnervesystemets kontrol af bevægelser og hvordan denne er forskellig mellem børn, unge og voksne. De bidrager også med en øget forståelse af hvad der i centralnervesystemet, når vi træner en ny motorisk færdighed, og hvordan dette er påvirket af alder. Disse fund er ikke kun interessante fra et grundforskningsperspektiv. De bidrager også med information, som på sigt kan hjælpe os med at udvikle og raffinere interventioner, der tilsigter at forbedre bevægelseskontrol og indlæring af motoriske færdigheder for mennesker med og uden motoriske udfordringer.

Manuscripts included in thesis

Manuscript I

Reorganization of functional and directed corticomuscular connectivity during precision grip from childhood to adulthood

Mikkel Malling Beck, Meaghan Elizabeth Spedden, Jesper Lundbye-Jensen

Manuscript in review. *Scientific Reports*.

Manuscript II

Cortical signatures of precision grip force control in children, adolescents, and adults

Mikkel Malling Beck, Meaghan Elizabeth Spedden, Martin Jensen Dietz, Anke Karabanov, Mark Schram Christensen, Jesper Lundbye-Jensen

eLife. 2021; (10); 10.7554/eLife.61018

Manuscript III

Distinct mechanisms for motor skill learning in children and adults

Mikkel Malling Beck, Frederikke Toft Kristensen, Gitte Abrahamsen, Meaghan Elizabeth Spedden, Mark Schram Christensen, Jesper Lundbye-Jensen

Manuscript in progress. Short Report. To be submitted to *Nature Neuroscience*.

Manuscript IV

Motor practice differentially modulates functional connectivity in cortical and corticospinal networks in children, adolescents and adults

Mikkel Malling Beck, Frederikke Toft Kristensen, Gitte Abrahamsen, Meaghan Elizabeth Spedden, Mark Schram Christensen, Jesper Lundbye-Jensen

Manuscript in progress. To be submitted to *Journal of Physiology*.

Thesis at a glance

Paper	Research question(s)	Methods	Main finding(s)
I	(i) Are there differences in corticomuscular control mechanisms between children, adolescents and adults during precision grip motor tasks? (ii) Are there differences in corticomuscular mechanisms for the control of the dominant hand and non-dominant hand and does this differ for individuals at different stages of development?	Corticomuscular coherence was estimated from EEG and EMG data from 115 individuals (age-range 8-30y) of different ages while they performed a precision grip motor task with both the dominant and non-dominant hand. Directionality analyses was used to decompose coherence into descending (cortex-to-muscle) and ascending (muscle-to-cortex) components.	(i) Yes. Greater coherence are observed for adults compared to children. This is due to a greater reliance of descending (cortex-to-muscle) connectivity. (ii) Yes. Greater coherence is observed on the non-dominant compared the dominant hand. The effect size is small and observed across the entire sample.
II	(i) How is connectivity in an extended cortical sensorimotor network associated with motor precision performance? (ii) How does cortical connectivity change with age and how does age modulate relationships between connectivity and motor precision?	Dynamic causal modeling (DCM) for cross-spectral densities was used to estimate effective connectivity from EEG data from 88 individuals (age-range 8-30y). Parametric empirical Bayes (PEB) was used to determine connectivity patterns related to age, performance and age-performance interactions.	(i) Skilled performance relates to connectivity in a canonical grasping circuit across age groups. (ii) From late adolescence, a greater degree of efficient top-down and executive control processes are used.
III	(i) Are there age-related differences in the behavioral changes during motor practice (*online; within-session*) and during subsequent consolidation (*offline; between-session*)?	Motor performance was evaluated at baseline, just after practice and 6 or 24 hours after practice to quantify *online (immediate retention-baseline)* and *offline* learning *(delayed retention-immediate retention)* in 119 individuals (age-range 8-30y).	(i) Yes. Adolescents and adults show larger *online (i.e. within-session)* improvements in performance, but children display greater *offline* (*i.e. between*-session) improvements in performance. Offline gains are observed overnight in children.
IV	(i) Are there age-related differences in the cortical and corticomuscular response to motor practice?	Non-zero lagged cortico-cortical and corticomuscular coherence was estimated before and after visuo-motor practice from source-reconstructed EEG and EMG data from 101 able-bodied individuals (age-range 8-30y). Control experiments were performed to evaluate whether changes were related to absolute skill level or to actual practice.	(i) Yes. Cortical and cortico-muscular coherence increases following motor practice, but this upregulation is predominantly seen in older adolescents and adults who practice the task. This co-varies with patterns of improvements in skilled motor performance (as observed in Manuscript III).