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Summary

Aging affects our central nervous system and, consequently, our physical capabilities. This can be seen, for instance, in slower movements compared to when one was younger. Motor training can limit age-related decline in motor functions, and various neuromodulation techniques might counteract age-related motor deficits even further. Developing optimal neuromodulation techniques to positively interact with motor training may help maintain motor function and independence through late adulthood, leading to healthier aging. Additionally, research in this area can also provide mechanistic insights.

In humans, the non-invasive brain stimulation technique paired corticospinal-motoneuronal stimulation (PCMS), can be used to target and subsequently modulate the efficiency of corticomotoneuronal (CM) synapses at the level of the spinal cord. Based on principles of spike-timing-dependent plasticity, repeated pairs of transcranial magnetic stimulation (TMS) and electrical peripheral nerve stimulation can be aimed to arrive at the level of the CM-synapses in a specific order- and timing. This technique has been shown to improve motor function in individuals with spinal cord injury. How PCMS interacts with motor practice has not been investigated, and whether the effects are different across age groups is also unknown. **Study I** of the present thesis investigates the effects of PCMS on ballistic motor learning and corticospinal excitability in young adults (20-30 years). **Study II** follows up showing that older adults (65-75 years) perform at a lower level, improve less with practice compared to young adults, and display low retention. The study also investigates whether PCMS can prime ballistic motor learning in older adults.

A more ecological and less specific neuromodulation approach is achieved with aerobic exercise. Notably, high-intensity aerobic exercise performed after a motor practice session has been shown to enhance motor learning in young adults. **Study III** builds upon previous findings from young adults, by investigating whether similar positive effects of exercise on learning can be observed in older adults.

Collectively, the three studies demonstrate that motor skill learning can be improved in young and older adults by combining motor practice with neuromodulatory interventions. Specifically, PCMS can induce plastic changes at the spinal level to prime ballistic motor learning, whereas acute aerobic exercise, when performed after motor practice, likely utilizes the physiological response to benefit processes of neuroplasticity during the memory consolidation phase.

Dansk Resume (Summary in Danish)

Aldring medfører ændringer i centralnervesystemet der påvirker ens funktionsniveau, eksempelvis udføres eksplosive bevægelser ofte langsommere med alderen. Motorisk træning kan mindske disse aldersrelaterede ændringer. Plasticitets-modulerende interventioner, kombineret med træning, kan muligvis bidrage til yderligere opretholdelse af funktionsniveauet hos ældre. Udvikling af interventioner, der kan forbedre udbyttet af motorisk træning, kan potentielt hjælpe med at bevare motoriske funktioner og dermed øge selvstændigheden i alderdommen, og dermed fremme sund aldring.

Hos mennesker kan den non-invasive stimulationsteknik *paired corticospinal-motoneuronal stimulation* (PCMS) målrettes og bruges til at modulere effektiviteten af corticomotoneuronale (CM) synapser på rygmarvsniveau. PCMS er baseret på principper fra *spike-timing-dependent plasticity*, og består af gentagne parrede sæt af transkranial magnet stimulation (TMS) og elektrisk perifer nerve stimulation, der indstilles til at ankomme til CM-synapseniveau i en specifik rækkefølge og timing. Denne teknik har vist at kunne forbedre motorisk funktion hos personer med rygmarvsskader. Det er ikke blevet undersøgt, hvordan PCMS interagerer med motorisk træning og hvorvidt effekterne er anderledes på tværs af aldersgrupper. **Studie I** fra denne afhandling undersøger effekterne af PCMS på indlæring af en ballistisk bevægelse, samt effekterne på excitabilitet i den corticospinale nervebane i unge voksne (20-30 år). **Studie II** følger op med en undersøgelse af forskelle i præstationsniveau og indlæring mellem unge og ældre voksne (65-75 år). Studiet undersøger herefter effekterne af PCMS på motorisk indlæring hos ældre voksne.

En mere anvendelig og mindre specifik intervention kan opnås med konditionstræning. Højintens aerob træning udført efter motorisk træning har vist at forbedre motorisk indlæring hos unge voksne. **Studie III** tager afsæt i tidligere resultater baseret på unge voksne, og undersøger om lignende positive effekter af konditionstræning på motorisk indlæring kan observeres i ældre voksne.

Afhandlingens tre studier viser at motorisk indlæring kan forbedres hos unge og ældre voksne ved at kombinere motorisk træning med forskellige plasticitets-modulerende interventioner. Non-invasive hjernestimulationer kan inducere plastiske ændringer i specifikke områder af centralnervesystemet, hvorimod højintens aerob træning medfører et fysiologisk respons, der kan gavne de processer, der ligger til grund for konsolidering af hukommelse efter læring.

List of publications

Study I

Hebbian priming of human motor learning

Jonas Rud Bjørndal, Mikkel Malling Beck, Lasse Jespersen, Lasse Christiansen & Jesper Lundbye-Jensen.

Nature Communications 2024; https://doi.org/10.1038/s41467-024-49478-5

Study II

Paired corticospinal-motoneuronal stimulation enhances ballistic motor learning and corticospinal plasticity in older adults

Jonas Rud Bjørndal, Lasse Jespersen, Mikkel Malling Beck, Anke Karabanov, Lasse Christiansen & Jesper Lundbye-Jensen

The Journal of Physiology 2024 (Submitted)

Study III

Acute exercise after motor practice enhances generalized skill learning, corticospinal excitability, and intermuscular coherence in older adults

Jonas Rud Bjørndal, Lasse Jespersen, Eva Rudjord Therkildsen, Rasmus Dam Wiedemann, Anke Karabanov & Jesper Lundbye-Jensen

Neurobiology of Learning and Memory 2024 (Submitted)

Thesis at a glance

	Motivation and Research Questions	Methods	Key Findings
Part I: Non-invasive brain stimulation as neuromodulation to prime ballistic motor learning in young and older adults			
Study I	Paired corticospinal-motoneuronal stimulation (PCMS) is a non-invasive technique used to modulate the efficiency of corticomotoneuronal synapses in humans. Proof-of-principle in young adults (age 20-30 years): Can PCMS be used to prime learning of ballistic movements relying on efficient corticospinal activation?	Experiment I: A between-group design. Participants were randomized to PCMS or Rest before practicing dynamic index finger flexions. Motor performance was quantified as peak acceleration. TMS was used to assess corticospinal excitability.	PCMS before motor practice led to superior motor learning compared to rest. Corticospinal excitability increased after PCMS and ballistic motor practice.
	Can the findings from Experiment I be replicated? Are the effects of PCMS superior to a SHAM protocol? Do PCMS and ballistic motor practice have a long-lasting behavioral effect?	Experiment II: A double-blinded SHAM-controlled between-group design. A 7-day retention test was added to test long-term effects.	Findings from Experiment I were replicated. PCMS led to superior learning compared to SHAM. Effects persisted one week later.
	How important are the timing aspect and ordering between stimulation in PCMS for learning? Do the effects of PCMS on learning adhere to Hebbian learning rules regarding timing-specificity and bidirectionality?	Experiment III: Within-subject cross-over study. Participants completed three sessions of PCMS before motor practice, spaced by a week.	PCMS with close timing (PCMS+) led to superior learning compared to the two asynchronous PCMS protocols (PCMS- and $PCMS_{coupled\text{-}control}$). Findings approximate Hebbian learning rules, since PCMS- decreased early learning.
Study II	Do the findings from Study I on young adults also apply to older adults (age 65-75 years)? Aging comes with a decline in many motor functions and shows smaller learning after practice, including ballistic movements. Does PCMS before ballistic motor practice improve motor learning compared to SHAM in an older population?	Similar experimental procedures as in Study I. The first part included a between-group comparison of behavioral data from older and younger adults. The second part compared the older SHAM group with and older PCMS group.	Part one: Older adults demonstrated lower ballistic motor performance, lower improvements with practice, and lower retention compared to young adults. Part two: PCMS led to superior motor learning compared to SHAM in older adults. Corticospinal excitability increased after PCMS and ballistic motor practice.
Part II: Effects of Motor Practice Followed by Exercise on the Consolidation of Visuomotor Skills in Older Adults			
Study III	Aging affects the learning of more complex visuomotor skills. Research in younger adults suggests acute exercise as an intervention capable of improving memory consolidation through its broad physiological effects. How does a single session of high-intensity aerobic exercise after motor practice affect visuomotor skill learning and memory in older adults?	Between-group design. Participants practiced a sequential-visuomotor tracking task followed by randomization to either high-intensity Exercise or Rest. Performance was assessed at later (delayed) retention tests. TMS was used to assess corticospinal excitability before and after interventions.	High-intensity aerobic exercise improved generalized motor learning, but not sequence-specific motor learning. Exercise prolonged motor practice-induced increases in corticospinal excitability. Change in corticospinal excitability correlated with total learning.