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Associations of Aging, Menopause, and Strength Training on Cortical Somatosensory and Motor Functions

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ABSTRACT

Healthy aging is associated with a decline in cognitive and physical functions, which are underpinned by changes in the structure and function of the brain and nervous system. This dissertation investigated the associations between aging and somatosensory-cognitive brain functions in young, middle-aged, and older adults, as well as the effect of long-term strength training on cognitive brain responses in aging utilizing magnetoencephalography (MEG). Furthermore, the dissertation examined the relationship between the stages of the menopausal transition (i.e. perimenopause) and neuromuscular excitatory and inhibitory mechanisms, employing transcranial magnetic stimulation (TMS) and peripheral electrical stimulation. The findings of *Study I* demonstrated possible alterations in TMS-induced inhibition and excitation in late perimenopausal women compared to early perimenopausal women. Additionally, a correlation was observed between follicle-stimulating hormone levels and twitch force potentiation, indicating a potential decline in muscle force potentiation mechanisms. The results suggest subtle modulation in neuromuscular mechanisms due to the menopausal transition. *Study II* indicated no differences in cognitive brain component P3b amplitude in strength-trained older men compared to their untrained controls. However, the results indicated a difference in the hemispheric cortical activity between the two groups. *Study III* implicated larger early somatosensory brain components (M100) to task-irrelevant stimuli in older adults compared to young adults. Older adults also exhibited reduced somatosensory change detection and attention-shifting mechanisms and altered cortical distribution in cognitive brain components. The results indicate a decline in the inhibition of somatosensory task-irrelevant stimuli and altered attentive and non-attentive change detection mechanisms in older adults compared to young adults. In conclusion, the results of this dissertation indicate that somatosensory brain components may serve as potential indicators of age-related cognitive decline and possible preventive mechanisms. Furthermore, menopausal transition, characterized by changes in hormonal balance, may already be exhibited in alterations in cortical and peripheral neural mechanisms.

Keywords: aging, change detection, event-related field, menopause, somatosensory system

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Kognitiivisen ja motorisen ikääntymisen taustalla on monenlaisia muutoksia niin aivojen kuin ääreishermostonkin rakenteissa ja toiminnassa. Tässä väitöskirjassa tutkittiin ikääntymisen ja tuntojärjestelmän aivovasteiden välisiä yhteyksiä nuorilla, keski-ikäisillä ja ikääntyneillä aikuisilla sekä pitkäaikaisen voimaharjoittelun vaikutuksia kognitiiviseen aivovasteeseen ikääntyneillä henkilöillä hyödyntäen magnetoenkefalografiaa (MEG). Lisäksi tutkittiin menopausaalisen siirtymän, eli perimenopaussin aikaisen hormonaalisen ikääntymisen yhteyttä hermolihasjärjestelmän inhibitoriseen, eli estävään ja eksitatoriseen, eli kiihdyttävään toimintaan transkraniaalisella magneettistimulaatiolla (TMS) sekä ääreishermoston sähköisellä stimulaatiolla. *Ensimmäisen tutkimuksen* tulokset osoittivat muutoksia TMS:lla aikaansaadussa inhibitorisissa ja eksitatorisissa vasteissa myöhäisen perimenopaussivaiheen naisilla verrattuna aikaisessa perimenopaussivaiheessa oleviin naisiin. Lisäksi havaittiin yhteys follikkelia stimuloivan hormonin tason sekä lihasnykäyksen potentoitumisen välillä. *Toisessa tutkimuksessa* ei havaittu eroa kognitiivisen P3b herätevasteen voimakkuudessa pitkäaikaista voimaharjoittelua tehneiden ikääntyneiden miesten ja samanikäisten ei voimaharjoitelleiden verrokkien välillä. Tulokset osoittivat kuitenkin ryhmien välisiä eroja herätevasteen voimakkuudessa eri aivopuoliskojen välillä. *Kolmannen tutkimuksen* tulokset osoittivat ikääntyneillä aikuisilla suuremmat lyhytlatenttiset herätevasteet (M100) tarkkaavaisuuden ulkopuolella olevissa ärsykkeissä nuoriin aikuisiin verrattuna. Lisäksi ikääntyneillä aikuisilla havaittiin pienempi tarkkaavaisuuden siirtymiseen liittyvä herätevaste (P3a) kuin nuorilla aikuisilla sekä frontaalisempi aivoaktivisuus kognitiivisen herätevasteen (P3b) aikana. Tämän väitöskirjan tulokset osoittavat muutoksia ikääntyneiden aivojen tuntoaistijärjestelmän inhibitorisessa toiminnassa sekä muutoksenhavaitsemisjärjestelmässä. Tulokset osoittavat, että tuntoaistijärjestelmän herätevasteet voivat olla mahdollisia ikääntymiseen liittyvien kognitiivisen toiminnan muutosten sekä ennaltaehkäisevien menetelmien luotettavia indikaattoreita. Lisäksi osoitettiin, että menopausaalisen siirtymän aikaiset hormonaaliset muutokset voivat heijastua aivojen ja lihashermojärjestelmän toimintaan.

Asiasanat: herätevaste, ikääntyminen, inhibitio, tuntoaisti, vaihdevuodet

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ORIGINAL PUBLICATIONS AND AUTHOR CONTRIBUTION

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

I   Pesonen, H., Laakkonen, E. K., Hautasaari, P., Aukee, P., Kovanen, V., Sipilä, S., Finni, T., & Tarkka, I. M. (2021). Perimenopausal women show modulation of excitatory and inhibitory neuromuscular mechanisms. *BMC Women's Health,* 21, Article 133. https://doi.org/10.1186/s12905-021-01275-8

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III   Pesonen, H., Strömmer, J., Li, X., Parkkari, J., Tarkka, I. M., & Astikainen, P. (2023). Magnetoencephalography reveals impaired sensory gating and change detection in older adults in the somatosensory system. *Neuropsychologia*, 190, Article 108702. https://doi.org/10.1016/j.neuropsychologia.2023.108702

As the first author of the original publications, considering the instructions and comments from the co-authors, the author of the thesis took the main responsibility of writing the manuscripts. With the help of my supervisors and colleagues, I also performed the data pre-processing and statistical analysis for all studies. In *Studies I* and *II*, the author played a significant part in the data collection. In *Study III*, the author was privileged to use pre-existing data.

FIGURES

TABLES

ABBREVIATIONS

AMH   Anti-Müllerian hormone
BDNF   Brain-derived neurotrophic factor
BMI   Body mass index
CMEP   Cervicomedullary motor evoked potential
CST   Corticospinal tract
E2   Estradiol
ECG   Electrocardiogram
EEG   Electroencephalography
EMG   Electromyography
EOG   Electro-oculogram
ERF   Event-related field
ERP   Event-related potential
fMRI   Functional magnetic resonance imaging
FSH   Follicle-stimulating hormone
GABA   Gamma-aminobutyric acid
HRT   Hormone replacement therapy
ICF   Intracortical facilitation
ICI   Intracortical inhibition
IGF-1   Insulin-like growth factor
ISI   Interstimulus interval
LNS   Letter-number sequencing
MEG   Magnetoencephalography
MEP   Motor evoked potential
MI   Primary motor cortex
MMN   Mismatch negativity
MMR   Mismatch response
MT   Motor threshold
MVC   Maximum voluntary contraction
PA   Physical activity
PET   Positron emission tomography
PFC   Prefrontal cortex
pRCL   Phosphorylation of myosin regulatory light chains
PTT   Peak twitch torque
RAVLT   Rey auditory verbal learning test
RM   Repetition maximum
RMS   Root mean square
RMT   Resting motor threshold
ROCF   Rey-Osterrieth complex figure test
RSS   Root sum square
SD   Standard deviation
SEF   Somatosensory evoked field
SI   Primary somatosensory cortex
SII   Secondary somatosensory cortex

sMMR	Somatosensory mismatch response
SP	Silent period
SQUID	Superconducting quantum interference device
tDCS	Transcranial direct current stimulation
tES	Transcranial electrical stimulation
TMS	Transcranial magnetic stimulation
TMT	Trail making test

CONTENTS

1 INTRODUCTION

Global human life expectancy is rising, and by the year 2050, the world's population of individuals aged 60 years or older will double (World Health Organization [WHO], 2022). Evident changes in brain structure, functional networks, and metabolism occur during healthy aging (for reviews, see Harada et al., 2013; Mattson & Arumugam, 2018; Reuter-Lorenz & Park, 2010) resulting in a decline in both cognitive abilities and motor function (Harada et al., 2013; Jauny et al., 2022). These changes significantly impact an individual's functional abilities and overall quality of life. In female aging, menopause is an inevitable aspect of the aging process. It has been demonstrated to accelerate several changes related to normal aging, including a decline in cognitive and muscle function (Bondarev et al., 2018; Tirkkonen et al., 2022). As a result of the increased life expectancy, women now typically spend approximately one-third of their life post menopause. Therefore, an investigation of the menopausal transition and the consequences of reproductive cessation is a crucial element of understanding female aging.

Regular physical exercise is regarded as a significant part of a healthy lifestyle, and it is shown to enhance both physical and brain health (for reviews, see Erickson et al., 2019; Hillman et al., 2008; Kujala, 2021; Pasanen et al., 2017). The benefits of exercise on cognitive function in older adults are reflected in the electrophysiological components of the brain, particularly in the context of physical activity (PA) and aerobic exercise (for reviews, see Kao et al., 2019; P. J. Smith et al., 2010) and physical fitness (Pontifex et al., 2009). Strength training provides a beneficial exercise method for older adults, as it has been demonstrated to maintain good functional capacity and quality of life (Ihalainen et al., 2019; Walker et al., 2014; for a review, see Kell et al., 2001). The long-term effects of strength training on markers indicating good brain function should be further investigated to promote effective training methods for the aging population.

Modern neuroimaging methods allow us to study the possible first markers of the normal aging process in the brain and peripheral nervous system and provide important information on the mechanisms behind cognitive and motor

deterioration. This dissertation investigates the effects of aging and hormonal aging on the neural mechanisms associated with cognitive abilities and motor function, specifically inhibition in both somatosensory and motor systems, excitatory mechanisms, and brain markers associated with cognitive function. This dissertation consists of three published scientific articles and this thesis summarizes the research findings.

2   LITERATURE REVIEW

2.1   Neuroimaging and neural stimulation techniques: Magnetoencephalography, transcranial magnetic stimulation, and peripheral electrical stimulation

Modern functional brain imaging and stimulation methods are widely used in research and clinical settings. The most notable functional brain imaging techniques include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetoencephalography (MEG) (Purves et al., 2019, p. 27). As fMRI, and to some extent PET, allow imaging with the highest spatial accuracy, MEG and electroencephalography (EEG) provide higher temporal accuracy to localize brain activity, to a sub-millisecond resolution. Combined with its relatively good spatial resolution, MEG is widely used to detect local brain activity changes over time in individuals performing various types of tasks (for a review, see Baillet, 2017). MEG has become a widely utilized experimental tool, but it has also been established in clinical practice, including applications in epilepsy surgery and functional brain mapping (Tiège et al., 2017). Nevertheless, further validation is necessary for its wider clinical utilization. The most utilized non-invasive brain stimulation methods include transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and transcranial direct current stimulation (tDCS) (Hallett, 2000; Reed & Cohen Kadosh, 2018). In TMS, a pulsed extracranial magnetic field produced by the coil induces intracranial electrical currents, whereas in tDCS, a constant electric flow is delivered to the brain via scalp electrodes (Hameed et al., 2017). While tDCS has shown its potential increasingly in recent years, TMS is currently the most utilized as an experimental tool, but also a diagnostic and therapeutic tool across various neurological and psychiatric disorders and conditions (Lefaucheur et al., 2014; Vucic et al., 2023).

As brain imaging offers a variety of ways to obtain images of living functioning brains in action, brain and neural stimulation enable the perturbation of neural information processing and the measuring of its effects on neural function or behavior (Baillet, 2017; Hallett, 2000). These methods allow us to

examine the central nervous system from two different perspectives, processing of afferent information and the effect of external perturbation on efferent processes.

2.1.1 Magnetoencephalography

Magnetoencephalography is a non-invasive functional brain imaging technique that measures the magnetic fields generated by electric currents in the human brain (Baillet, 2017; Hari & Puce, 2017, pp. 6-9). MEG signals were first measured by Cohen in the 1960s (Cohen, 1968), and they provide information on the dynamics of the events of neural populations in the cerebral cortex. Compared to its close relative EEG, MEG can detect independent sources of the current flow, without reference to other currents, thus providing rather good spatial resolution in the range of a few mm (Hari & Puce, 2017, pp. 6-11). Combined with its high temporal resolution, MEG provides a tool to study local activity changes millisecond by millisecond in individuals during task performance, as well as the baseline activity before task initiation and activity after task completion (Purves et al., 2019, p. 28).

The main origin of MEG signals is the postsynaptic activity of the pyramidal neurons on the cerebral cortex, which are aligned perpendicularly to the cortical surface (Baillet, 2017). With their long apical dendrites, the pyramidal neurons produce intracellular currents and coherent magnetic fields when they activate with a certain amount of synchrony. Most of the signals that are detectible by MEG arise from pyramidal neurons in the walls of cortical fissures, as currents aligned tangential to the skull surface produce magnetic fields that are detectable outside the skull (Figure 1). This is an advantage, as the fissures comprise about two thirds of the entire cortex, including the primary sensory cortices (Hämäläinen et al., 1993; Hari & Puce, 2017, pp. 6-11). In addition, magnetic fields are mainly unaffected by tissues between the brain and MEG sensors, such as the scalp and skin. Deep sources are more difficult to detect with MEG due to the longer distance between the source and sensors. However, the potential of measuring deeper sources with MEG has also been suggested (Baillet, 2017; Samuelsson et al., 2019).

The state-of-the-art commercial MEG systems have up to 306 magnetic field sensors, with the superconducting quantum interference device (SQUID) sensors the flux transformers, and the cryogenic vessel ("dewar"), that contains liquid helium, as the main components (Hari et al., 2018). The SQUID measuring system is susceptible to surrounding magnetic noise, such as the earth's geomagnetic field fluctuations, the power-line fields, and everyday electric devices. This is controlled by the proper design of the flux transformers that couple the neuromagnetic field to the SQUIDs, but also by performing measurements in a magnetically shielded room (Hämäläinen et al., 1993; Hari et al., 2018).

Regardless of MEG's technically demanding characteristics, it has proven a beneficial method, as it is a non-invasive and versatile tool to study human brain function dynamics in research and increasingly in clinical settings (Hari et al., 2018). Given its high temporal accuracy, MEG is suitable for studying brain

function close to sensory stimulation events. As EEG is commonly utilized to study event-related potentials (ERPs), MEG can be employed to detect magnetic even-related fields (ERFs) to image the activity of neural populations in response to stimulation events (Baillet, 2017).
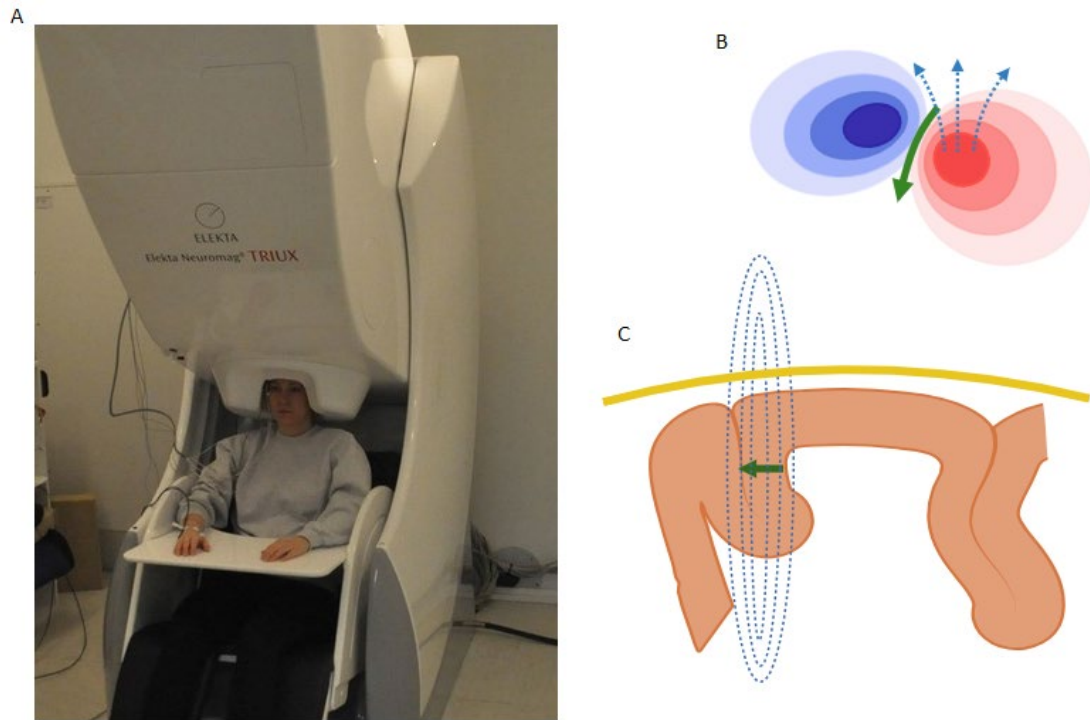
FIGURE 1   Illustration of the principles of magnetoencephalography (MEG) registration. (A) MEG devise with a person seated with their head inside the MEG helmet containing 306 magnetic field sensors. (B) MEG can detect the magnetic field created by electric current flow in the brain. (C) Detectable magnetic fields are generated by pyramidal neurons in the walls of cortical fissures as they are aligned perpendicular to the cortical surface. Created with BioRender.com.

2.1.2   Transcranial magnetic stimulation

Transcranial magnetic stimulation is a non-invasive, pain-free method for stimulating the human brain (Hallett, 2000). In 1985, Barker et al. first introduced that it was possible to stimulate the brain using magnetic stimulation (Barker et al., 1985). In TMS, a momentary high-intensity magnetic field is generated, by producing a brief pulse of electric current through a magnetic coil placed on the head above the target cortical area (Hallett, 2007). This magnetic field then induces an electric field in the brain depolarizing neurons in the cortical tissue (Figure 2). The coil geometry, placement, and size, together with the subject's anatomy all affect the electric field distribution in the cortex (Paulus et al. 2013; Säisänen, Julkunen, et al., 2008). The most used coil shapes are circular and figure-of-eight coils. While circular coils are relatively powerful, figure-of-eight

coils are more focal as they produce maximal current at the intersection of two round components (Hallett, 2007).

The most common sequences to deliver TMS are single-pulse, paired-pulse, and repetitive TMS (Hallett, 2007). When applied to the primary motor cortex (MI), single-pulse TMS is most utilized to study variables such as motor threshold (MT), motor evoked potential (MEP), and silent period (SP), and is a very safe method (Rossini et al., 2015). MT is a measure of neuronal excitability, and it is used as a measure of stimulus intensity when studying the other variables. It is usually defined as resting MT (RMT) as the lowest intensity to induce an electromyogram (EMG) response, MEP, in the targeted, relaxed muscle, usually at the level of 5 times out of 10 consecutive stimuli (Rossini et al., 2015). However, it should be noted that these guidelines are based on upper limb musculature. Because the representative MI area for lower limb muscles is located more deeply in the median longitudinal fissure, these determinants may not be as easily applied, and inter-individual variability in the shape and size of gyri and sulci within the lower limb MI may pose a challenge in finding MTs and stimulation locations for target muscles (Kesar et al., 2018; Tarkka et al., 1995).

Motor evoked potential is induced, when TMS is delivered to the contralateral MI area of the targeted muscle (Säisänen, Julkunen, et al., 2008). It can be observed in the EMG of both resting and activated muscles. MEP amplitude is highly dependent on the contraction intensity of the target muscle (Säisänen, Pirinen, et al., 2008). It is a measure of the corticospinal motor neuron excitability and integrity of the corticospinal tract (CST), which is the pathway that connects the cerebral cortex to the lower motor neurons in the spinal cord. Although the interindividual variability of the MEPs is quite high, it is well utilized for example in the pre-surgical mapping of the motor cortex (Säisänen et al., 2010).

Silent period is a visible suppression of ongoing muscle activity in the EMG signal after MEP occurrence (Inghilleri et al., 1993; Säisänen, Pirinen, et al., 2008). SP can be used to measure corticospinal inhibition during voluntary contraction, and it is thought to be mediated by inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), particularly by GABA$_B$ receptors (Stetkarova & Kofler, 2013; Werhahn et al., 1999). The early part of SP (around 50 ms) is thought to arise from spinal origins, and the latter part from cortical origins (Cantello et al., 1992; Fuhr et al., 1991; Pierantozzi et al., 2004; Wilson et al., 1993; Ziemann et al., 1993). This theory was later questioned by Yacyshyn et al. (2016), who found spinal inhibitory modulation at even 150 ms after stimulation. However, the SP duration is shown to be related to cortical oscillatory activity and N1 component amplitude in EEG recordings (Farzan et al. 2013). The roles of spinal and cortical mechanisms in the latter part of SP remain debated and should be further investigated (for a review, see Hupfeld et al., 2020). The challenge in SP is that it has high inter-individual variability. It is also highly affected by stimulus intensity and muscle force (Säisänen, Pirinen, et al., 2008). However, SP duration is shown to be modulated in several clinical conditions, including schizophrenia

(Daskalakis et al., 2002), stroke (Classen et al., 1997), epilepsy (Kim et al., 2008), and Parkinson's disease (Priori, 2009).
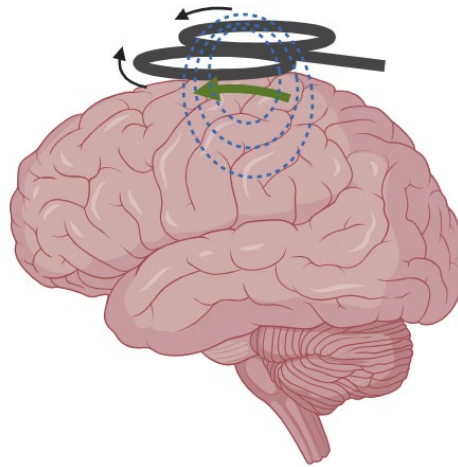
FIGURE 2   Schematic illustration of transcranial magnetic stimulation (TMS) application. The figure-of-eight coil applied on the cortex creates a magnetic field (blue dashed line) in the brain, which induces an electric current (green arrow) in the cortex. Created with BioRender.com.

2.1.3   Peripheral electrical stimulation

Peripheral electrical nerve stimulation is a technique, in which electrical current is applied to peripheral nerves through electrodes placed on the skin surface. The application of a voltage that induces an electrical current flow across the membrane of the axon results in the depolarization of the nerve membrane and the subsequent generation of an action potential – i.e., activation of the nerve fiber (Swett & Bourrassa, 2013). It is used in both clinical and research applications, including rehabilitation, chronic pain management, and neurophysiological studies (Finni et al., 2011; Helm et al., 2021; Zainea et al., 2005; for reviews, see Costello et al., 2023; Pascual-Fernández et al., 2020). Electrical stimulation is a valuable tool for investigating the neural mechanisms underlying motor function and associated changes in healthy and clinical conditions. Brief stimulation of a peripheral nerve at an individually determined threshold results in a single contraction, i.e. a muscle twitch. In neuromuscular research, electrical stimulation is used to investigate a range of physiological processes, including the properties of motor units, diverse muscle fibers, and force production (Finni et al., 2011; Mancinelli et al., 2019; Tarkka, 1986).

2.2   Somatosensory processing and event-related fields

The somatosensory system involves those peripheral and central components that process information conveyed by mechanical stimuli that either impinge the

body surface (cutaneous mechanoreception) or originate within the body itself (proprioception) (Purves et al., 2019, p. 181). Somatic sensation initiates from the encapsulated afferent nerve endings, mechanoreceptors, located in the skin or subcutaneous tissue, which react to certain features of somatic stimulation: touch, pressure, vibration, and cutaneous tension. A stimulus alters the permeability of cation channels in the peripheral afferent nerve endings, generating a depolarizing current, receptor potential, in the nerve (Purves et al., 2019, pp. 181-182; Strominger et al., 2012a). The cell bodies of peripheral afferent nerves are located in the dorsal root ganglia, where their heavily myelinated fibers, mostly fast conducting Aβ afferents, continue entering the spinal cord through the dorsal roots (Strominger et al., 2012a). The main afferent fibers will extend ipsilaterally through the dorsal white column of the spinal cord as a gracile tract and a cuneate tract, for lower and upper body nerve fibers, respectively. These are called first-order neurons. They extend up to the brainstem, to the dorsal column nuclei (i.e. gracile nucleus and cuneate nucleus) in the medulla, and synapse with the second-order neurons. The second-order neurons form the internal arcuate tracts that cross the midline and then form an ascending tract known as the medial lemniscus. The axons of the medial lemniscus continue extending to the ventral posterior lateral (VPL) nucleus in the thalamus, where they synapse with the final third-order neurons. The third-order neurons extend through the internal capsule to the primary somatosensory cortex (SI) and the secondary somatosensory cortex (SII; Purves et al., 2019, p. 182; Strominger et al., 2012a). SI is located in the postcentral sulcus and includes representations of the body surface in somatotopical order (Figure 3; Purves et al., 2019, p. 190).

The somatosensory cortical function can be studied with MEG in experiments where a specific somatosensory stimulus or stimulus sequence is applied, and cortical brain activity is measured as somatosensory evoked fields (SEFs) in MEG registration (counterpart for somatosensory evoked potential, SEP, for EEG). Compared to other highly studied sensory modalities; vision and hearing, it is challenging to reproduce natural stimuli related to touch in laboratory settings. Therefore, electrical stimulation of peripheral nerves is a common method to elicit somatosensory responses (Hari & Forss, 1999; Hari & Puce, 2017, p. 68). Typically, electrical stimulation is applied over a peripheral nerve bundle (e.g. median nerve) activating the nerve fibers below the stimulation site, rather than mechanoreceptors. This results in SI responses earliest at 20 ms latency and SII responses earliest at 100 ms latency (Hari & Forss, 1999). On the other hand, electrical stimulation applied to the skin activates most of the nearby mechanoreceptors. Compared with nerve stimulation, responses are usually somewhat smaller in amplitude and their latencies are delayed due to skin receptor transduction time (Jousmäki, 2000). Generally, the early sensory ERF or ERP waves peaking approximately within 100 ms after stimulus presentation, are characterized as sensory, exogenous brain responses, as their characteristics are highly dependent on the physical features of the stimulus. The ERFs and ERPs occurring at later parts are considered cognitive, i.e. endogenous, and reflect the stimulus evaluation processes (Sur & Sinha, 2009).
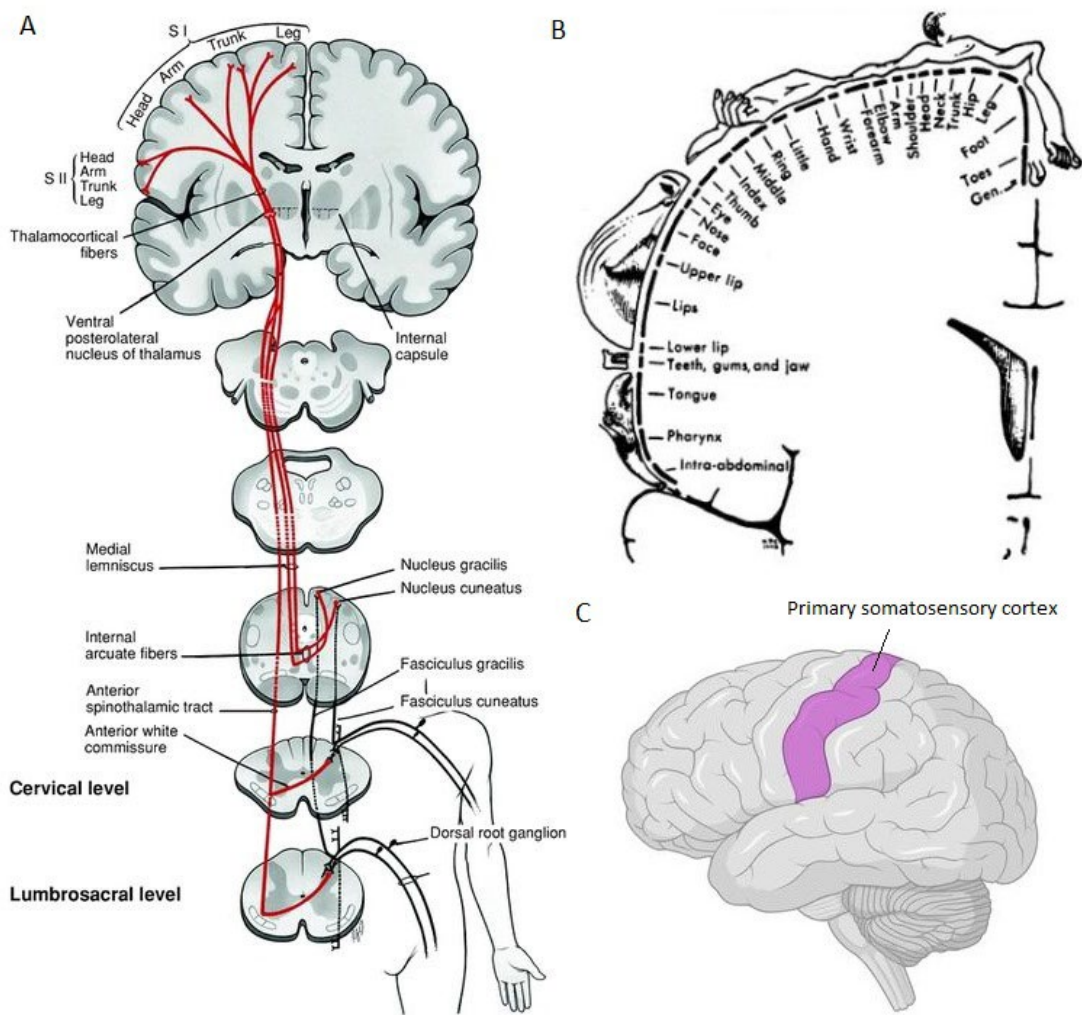
FIGURE 3   Illustration of the somatosensory pathways and the location and somatotopic organization of the primary somatosensory cortex (SI). (A) The somatosensory pathways comprise the dorsal column–medial lemniscus pathway and the anterior spinothalamic tract, which mediates crude touch and movement sensation. Pathways originate in the spinal cord and reach the SI and secondary somatosensory cortex (SII). Reprint from Strominger et al., 2012a. (B) Somatosensory homunculus after Penfield and Rasmussen (1950), with somatotopic representation for each body part in the SI. (C) The SI is located in the postcentral sulcus. Created with BioRender.com

2.3 Motor system

2.3.1 Corticospinal tract and lower motor neuron

The human motor system is a complex network of hierarchical neural circuits that together control both voluntary and involuntary movements. CST is the pathway that connects the cerebral cortex to the lower motor neurons in the spinal cord, allowing the fine-tuning and control of voluntary movements of the body. Most fibers of the CST originate from pyramidal cells and Betz cells of the somatotopically organized MI and supplementary motor area, and parts of the parietal cortex. They are called the upper motor neurons. The axons of the neurons descend through the ipsilateral posterior limb of the internal capsule, the crus cerebri in the midbrain, and the pons, where they are scattered among the transverse pontine fibers and nuclei of the basal pontine gray matter (Purves et al., 2019, p. 362). Subsequently, they merge again and descend through the pyramids of the medulla. From the axons that descend from the medulla to the junction before the spinal cord, approximately 90 % cross the midline to the contralateral posterior half of the lateral white column of the spinal cord, where they descend as the lateral CST. Approximately 10 % of the axons continue descending in the ipsilateral anterior white column of the spinal cord as the anterior CST and cross the midline to reach the contralateral ventral horn (Purves et al., 2019, p. 363; Strominger et al., 2012b). The anterior CST arises primarily from the dorsal and medial regions of the motor cortex, which control the trunk and proximal limb muscles. The lateral CST terminates primarily in the lateral portions of the ventral horn. Some of these axons synapse directly on α motor neurons, mainly for the forearm and hand. However, most axons terminate among pools of local circuit neurons that coordinate the activities of the lower motor neurons in the lateral cell columns of the ventral horn, innervating different muscles (see Figure 4; Purves et al., 2019, p. 363).

The lower motor neurons serve as the final link between the central nervous system and skeletal muscles. Their cell bodies lie in the ventral horn of the spinal cord for the upper and lower body, and the motor nuclei of the brainstem for cranial nerves (Purves et al., 2019, p. 337; Strominger et al., 2012b). Lower motor neurons that innervate skeletal muscle voluntary contractions are called α motor neurons, with heavily myelinated, fast-conducting axons that terminate in motor end plates of extrafusal striated muscle fibers. The intrafusal striated muscle fibers of the muscle spindles are innervated by γ motor neurons, with lightly myelinated, slow-conducting axons (Strominger et al., 2012b). A single α motor neuron and the muscle fibers it innervates form a motor unit. The fibers that one α motor neuron innervates can range from only a few to 2000 in different muscles. Usually, they branch within muscles to distribute over a wide area (Strominger et al., 2012b). Small motor neurons, with a small number of fibers they innervate, also usually comprise small muscle fibers that are resistant to fatigue. These are referred to as slow motor units (S) and are crucial for maintaining sustained muscle contraction, such as that required for maintaining posture. Larger motor

neurons innervate larger muscle fibers, exerting greater force. These are referred to as fast fatigable motor units (FF). They are important in more brief contractions, such as in jumping or fast running. The more intermediate-sized motor units are called fast fatigue-resistant (FR) motor units, which generate twice the force of slow units, but are resistant to fatigue (Gardiner, 2011; Purves et al., 2019, p. 342). The motor units are recruited according to the size principle, where weak synaptic input results in the recruitment of the smallest motor units, and with increasing synaptic input, progressively larger motor units are recruited. This phenomenon is found to occur with both stimulating peripheral nerves and upper motor pathways projecting to lower motor neurons, as well as voluntary and reflexive movements (Purves et al., 2019, p. 343).
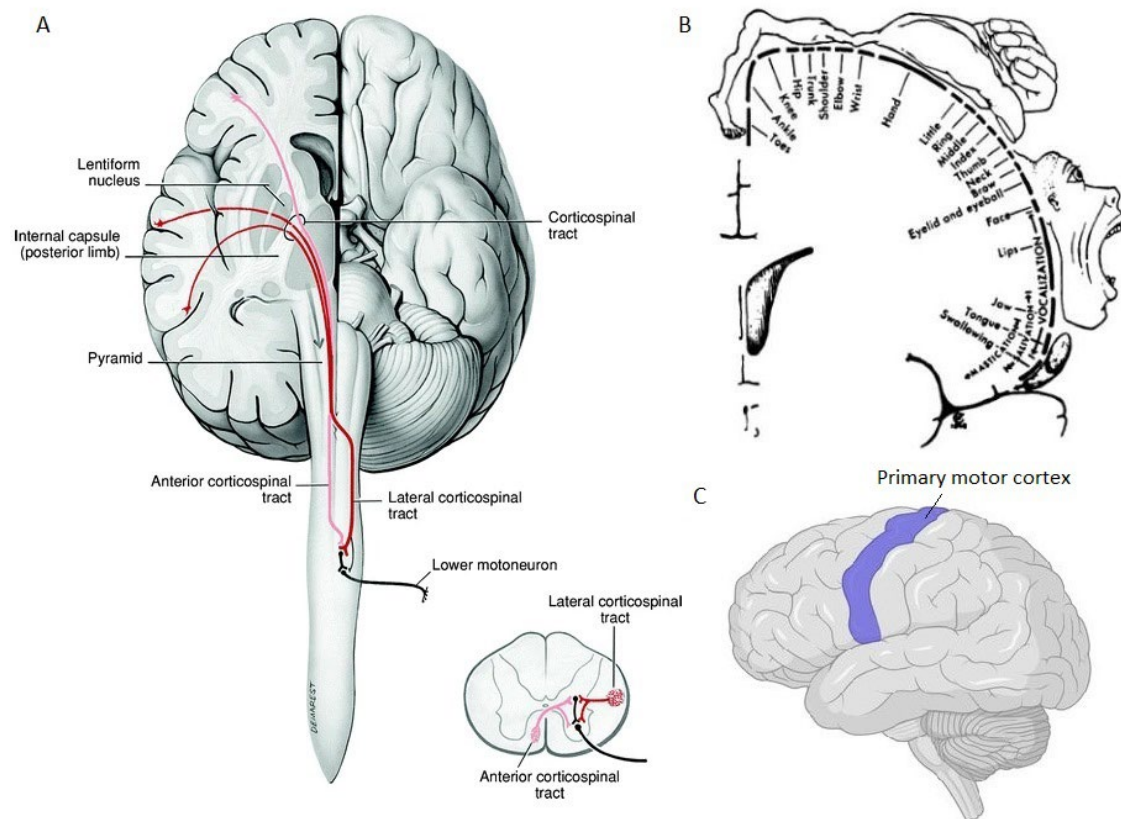
FIGURE 4   Illustration of the corticospinal tract (CST) and the location and somatotopic organization of the primary motor cortex (MI). (A) CST, comprising both anterior and lateral CSTs, originates from the cerebral cortex and reaches lower motor neurons in the spinal cord. Reprint from Strominger et al., 2012b. (B) Motor homunculus after Penfield and Rasmussen (1950), with somatotopic representation for each body part in the MI. (C) The location of the MI in the postcentral sulcus. Created with BioRender.com

2.4 Effects of aging on the brain and nervous system

Normal aging is well-established to be associated with structural and functional changes in the brain, such as volume reduction in both white and grey matter, synaptic decline, and neuronal network dysfunctions (Harada et al., 2013; Khalilian et al., 2024; Reuter-Lorenz & Park, 2010). This is shown to result in measurable changes in the cognitive and motor function of aging individuals (for reviews, see Hedden & Gabrieli, 2004; Reuter-Lorenz & Park, 2010; Seidler et al., 2010). In both motor and cognitive tasks, aging adults have been shown to have reduced inhibitory mechanisms and to recruit additional cortical and pre-cortical brain areas for task performance compared to young adults (Reuter-Lorenz & Park, 2010; Seidler et al., 2010). However, the underlying mechanisms are complex and remain debated to date.

2.4.1 Aging and brain electrophysiological markers

Cognitive function has been shown to decline most significantly in tasks that require selective attention, attention shifting or quickly processing or transforming information to make decisions (Lezak, 2012, p. 402). The ability to filter out irrelevant information and detect changes in the surrounding environment is a critical component of attention and information processing, as the human sensory systems are constantly bombarded with sensory information from the outside world. In laboratory settings, this phenomenon has been studied extensively using an experimental design called the oddball paradigm (Friedman, 2011; Figure 5). In this design, a continuous stimulus (standard) is less frequently replaced by an oddball stimulus (deviant). For example, in the somatosensory modality, electrical stimulation intensity and location are examples of stimulus characteristics used for stimulus change, however, a wide variety of different stimulus types have also been used in auditory, visual, and even olfactory sensory designs in the literature. To date, the oddball paradigm has been utilized extensively in both active (attended) and passive (non-attended) experimental designs to investigate cognitive processes, including perception, attention, context updating, and automatic change detection, mostly in the auditory and visual modalities (Anderer, et al., 1996; Astikainen et al., 2008; Bolton & Staines, 2012; Friedman, 2011; Hautasaari et al., 2019; Tarkka et al., 1996). However, the relationship between aging and somatosensory abilities remains understudied.
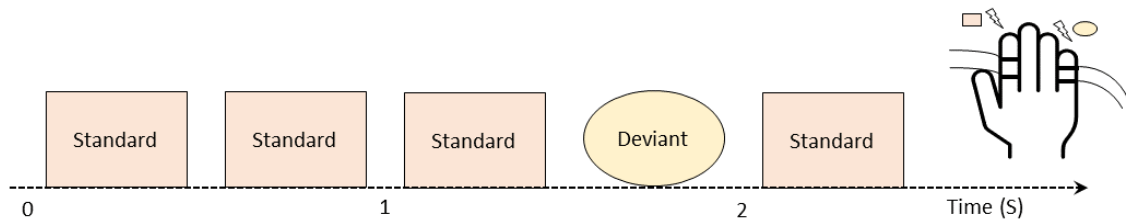
FIGURE 5   Example of an oddball experimental paradigm in which somatosensory electrical stimulation is applied to the fingers. The standard stimulus (index finger stimulation) is repeatedly presented and randomly replaced by the deviant stimulus (little finger stimulation).

2.4.1.1   Aging and change detection mechanisms

Early theories of change detection have emphasized the importance of focal attention to detect changes in the sensory environment (for a review, see Rensink, 2002). To date, several studies have demonstrated that the brain is capable of detecting even small changes that violate our automatic, non-conscious expectations (for reviews, see Czigler & Kojouharova, 2022; Näätänen et al., 2007; Stefanics et al., 2014). Mismatch negativity (MMN) is an ERP component that was first discovered in the auditory modality as a difference wave from 150 ms to 250 ms latency occurring after deviant stimuli in a passive oddball experimental design (Näätänen et al., 1978). After its discovery, MMN has been further confirmed in visual, somatosensory, and olfactory modalities (Astikainen et al., 2008, 2013; Hautasaari et al., 2019; Krauel et al., 1999; Kreegipuu et al., 2013; Strömmer et al., 2014; Xu et al., 2021). MMN is explained by the memory trace theory, where MMN is a result of memory trace comparison of standard and deviant input. The theories further suggest that MMN is a result of a prediction error in the brain's hierarchical sensory processing (for a review, see Garrido et al., 2009). This interpretation is based on predictive coding theory (Friston, 2005), which proposes that the brain makes constant predictions about the surrounding sensory environment based on previous sensory input. An unexpected (deviant) input then creates a prediction error that is further projected to higher levels of hierarchical networks to update the prediction further. An important feature of the MMN is that it is elicited outside of attention, and in passive oddball designs, participants are presented with a task that distracts their attention away from the given stimuli (e.g., an auditory radio play during a visual experiment; for a review, see Näätänen et al., 2007). In the somatosensory modality, the MMN has often been referred to as the mismatch response (MMR) due to its positive polarity in EEG registration. To date, somatosensory MMR (sMMR) has been found to occur for deviations in stimulus location, intensity, duration, and vibratory frequency for both EEG and MEG registrations (Akatsuka et al., 2005, 2007; Hautasaari et al., 2019; Kekoni et al., 1997; Naeije et al., 2016, 2018; Spackman et al., 2010; Strömmer et al., 2014). The neural generators of sMMR have been localized to SI and SII cortices (Akatsuka et al., 2007; Hautasaari et al., 2019; Naeije et al., 2018).

Several studies have investigated the relationship between aging and auditory MMN, and there is substantial evidence of age-related deterioration in MMN amplitude (for review and meta-analysis, see Cheng et al., 2013). A few studies have also reported prolonged latency in aging adults (Bertoli et al., 2002; Gaeta et al., 2001). These findings suggest that preattentive change detection is less sensitive in older adults than in young adults. However, there are relatively few age-related studies of MMN in other sensory modalities. There is some evidence for age-related deterioration of MMN amplitudes in the visual system (Tales et al., 2002; Tales & Butler, 2006), and reduced sMMR amplitudes in older adults compared to young adults have also been demonstrated in two studies by Strömmer et al. (2014, 2017) using EEG recordings. To my knowledge, there are no other studies investigating sMMR in older adults and none in the MEG setting.

2.4.1.2 Aging and P3 components

The oddball paradigm is widely used in the EEG literature to study P3, also known as the P300, an ERP component that is associated with processes related to attention, memory, and decision-making. The P3 component is typically observed in EEG registrations as a centro-parietally recorded positive waveform, occurring approximately 300 ms after stimulus presentation. The P3 was first reported nearly 60 years ago by Sutton et al. (1965). It has since been further subdivided into subcomponents called P3a and P3b (for a review, see Polich, 2007) and can be studied in all sensory modalities. The P3a component is elicited when the presented stimulus is either novel or in a passive oddball paradigm, wherein the deviant stimulus is intentionally ignored (Friedman et al., 1993, 2001; Polich, 2007). It is hypothesized to represent processes of stimulus evaluation and the orientation of attentional resources (for review, see Friedman et al., 2001). The origins of P3a have been located in the frontal lobe, hippocampus, and anterior cingulate cortex, and it is observed as more frontal cortical activation compared to the centro-parietal distribution of P3b (Knight, 1996; Wronka et al., 2012). The P3b is observed in an active oddball paradigm when attention is present. This is usually achieved by using an active task, such as responding (e.g., by pressing a button) to each of the presented deviant stimuli. It is associated with cognitive processes involved in updating working memory and allocating attentional resources (for a review, see Polich, 2007). The P3b has been extensively studied in many age groups and its characteristics have been associated with a variety of cognitive traits, including cognitive decline (Bennys et al., 2007; Deiber et al., 2015). The P3 represents activations of widespread neural circuits, and thus the localization of specific neural generators has been difficult. In young adults, various neural generators have been found to contribute to P3b generation across modalities, mainly located in the parietal and cingulate cortices (for a review, see Linden, 2005). In the somatosensory experiments, the neural generators of P3b have been located in the bilateral temporoparietal, hippocampal, parahippocampal, thalamic, frontal, and supplementary motor areas (Huang et al., 2005; Naeije et al., 2016; Tarkka et al., 1996; Valeriani et al., 2001).

The P3b component is probably the most studied electrophysiological component in relation to aging (for reviews, see Friedman, 2011; Polich, 1996; van Dinteren et al., 2014b). The most reported features are a gradually decreasing amplitude and increasing latency from young adulthood to old age (van Dinteren et al., 2014b). Another consistent finding is the frontally oriented scalp distribution in older adults compared to the parietal distribution of P3b in young adults (van Dinteren et al., 2014a). A study by van Dinteren et al. (2014a) further demonstrated that parietal P3b amplitude increases from childhood until adolescence and then decreases gradually for the rest of the lifespan. In contrast, frontal amplitude exhibits an increase until approximately 46 years of age, after which it remains relatively stable. Furthermore, studies have shown that older adults exhibit greater P3b activation in the precentral gyrus and the parahippocampal gyrus than young adults (van Dinteren et al., 2018). The P3a component has shown similar frontal distribution in older adults compared to young adults, with indications of a diminished amplitude (Fjell & Walhovd, 2003; Friedman, 2011; Gaeta et al., 1998). The functional significance of the age-related frontal shift in P3 activity remains to be fully elucidated. It has been proposed that it reflects the compensatory mechanisms of the aging brain to enhance cognitive function, however, it may be, that older adults merely recruit more cortical activity for task completion (Kamp, 2020; Kang et al., 2022; Reuter-Lorenz & Park, 2010; van Dinteren et al., 2014a). Therefore, further research is needed to fully understand the functional significance of the frontal shift of P3.

2.4.1.3   Aging and sensory inhibition

Sensory inhibition, or sensory gating, is a neurological mechanism that enables the brain to filter out and attenuate task-irrelevant or redundant sensory stimuli (Boutros et al., 1995; Boutros & Belger, 1999; Jones et al., 2016). Sensory gating is crucial for cognitive functions, such as attention, learning, and memory, as it prevents sensory overload and allows the brain to allocate resources to the task at hand (Friedman, 2011; Jones et al., 2016). Inhibitory mechanisms have been demonstrated to arise from prefrontal cortical (PFC), basal ganglia, and thalamic pathways (Gisiger & Boukadoum, 2011; Nakajima et al., 2019). In electrophysiological recordings, it is typically studied with a paired-stimulus paradigm, where two identical stimuli are presented with a short inter-stimulus interval (ISI), and sensory gating is observed as attenuation in the amplitude of the early brain responses for the second stimulus (Rentzsch et al., 2008). Sensory gating has been extensively studied and reported to be impaired in patients with schizophrenia, and later in other neuropsychiatric disorders such as bipolar disorder and depression (Boutros et al., 1999, 2004; Lijffijt et al., 2009; Ruohonen et al., 2020; Wang et al., 2009). Sensory gating is also shown to be impaired in aging individuals in early ERPs and ERFs in studies utilizing paired-pulse paradigm (Cheng, Baillet, et al., 2015; Cheng, Chan, et al., 2015; Terrasa et al., 2018). According to the inhibition deficit hypothesis, the ability to inhibit task-irrelevant sensory information declines with age (Arif et al., 2023; Hasher & Zacks, 1988; Kang et al., 2022; Lustig et al., 2007). By disrupting the ability to

process task-relevant information, impaired inhibition has been suggested as one of the main mechanisms underlying age-related cognitive decline (Gazzaley et al., 2005; Hasher, 2015; Reuter-Lorenz & Park, 2010).

Sensory gating can also be observed in oddball conditions, as attenuation of the early brain responses (mainly P50 or N100 studied in the auditory modality) to standard (frequent) stimuli (Alain & Woods, 1999; Anderer et al., 1996; Boutros et al., 1995; Ruohonen et al., 2020; Stothart & Kazanina, 2016). Oddball experiments have also demonstrated impaired sensory gating in older adults, primarily as larger P50 and/or N1 components for repetitive stimuli, predominantly in the auditory modality (Alain & Woods, 1999; Amenedo & Díaz, 1998a; Anderer et al., 1996; Bennett et al., 2004; Ruohonen et al., 2020; Stothart & Kazanina, 2016). In contrast, some studies have failed to identify group differences between young and older adults in auditory N1 (Bertoli et al., 2002; Čeponienė et al., 2008; Friedman et al., 1993; Gaeta et al., 1998). However, there is evidence of increased auditory N1 amplitude for repetitive stimuli already in middle-aged adults (Amenedo & Díaz, 1998b; Anderer et al., 1996). Studies in the somatosensory domain are still relatively limited. A study by Strömmer et al. (2017) found larger P50 and N80 amplitudes in a passive oddball paradigm for both standard and deviant stimuli in older adults compared to young adults. However, this difference was not significant after controlling for stimulus intensity, which was higher in older adults than in young adults. Bolton and Staines (2012) also found diminished suppression of standard P100 amplitudes in older adults compared to young adults. Furthermore, no difference was found for the attended standard P100 when the participant's attention was focused on the standard stimuli. The only study to investigate this phenomenon in middle-aged adults was conducted by Reuter et al. (2013), which failed to find differences in amplitudes. To my knowledge, no other oddball studies have investigated the relationship between somatosensory inhibition and aging.

2.4.2 Neuromuscular mechanisms of aging

Aging is associated with declines in motor performance and function, such as muscle power, strength, velocity, and increased fatigability, which affect older adults' activities of daily living and independence and increase the risk of falls (for reviews, see Hunter et al., 2016; Moreland et al., 2004). The underlying mechanisms are multifactorial and include changes in the central and peripheral nervous system, muscle structure, and physiology.

As described above, the aging brain undergoes various changes in cortical structure and function, and these changes also affect the neuromuscular system. Similar to cognitive functions, brain motor cortical areas have also shown a decrease in inhibitory mechanisms and an increase in activity in certain cortical regions (for reviews, see Hunter et al., 2016; Seidler et al., 2010). For example, TMS studies have shown reduced interhemispheric inhibition and reduced short interval intracortical inhibition in older adults compared to young adults (Heise et al., 2013; Marneweck et al., 2011; Mattay et al., 2002; Talelli et al., 2008). In addition, there is evidence for reduced corticospinal inhibition, expressed as

shorter TMS-induced SPs, in older adults compared to young adults (Christie & Kamen, 2014; Oliviero et al., 2006; M. V. Sale & Semmler, 2005), also after fatiguing exercise (Hunter et al., 2008). However, some studies found no change in SP duration (Fujiyama et al., 2009, 2012; Säisänen, Julkunen, et al., 2008) or even longer SP in older adults than in young adults (Gomez-Guerrero et al., 2024). Lower GABA levels have been reported in older adults compared to young adults, with an association between lower GABA levels in the pre-supplementary motor area and decreased reactive motor inhibition (Hermans et al., 2018). In addition, increased activity in motor cortical regions has been shown for both ipsilateral and contralateral hemispheres during motor tasks in aging adults (Mattay et al., 2002; Ward, 2006). Yet, older adults have also shown reduced MEP amplitudes compared to young adults (Fujiyama et al., 2012; Oliviero et al., 2006; M. V. Sale & Semmler, 2005).

Aging is associated with considerable changes in motor units, muscles (for reviews, see Porter et al., 1995; Verschueren et al., 2022), and associated neural pathways (Tomlinson & Irving, 1977). The number of motor neurons in the spinal cord decreases with advancing age, resulting in a decrease in the number of functioning motor neurons. In addition, the neuromuscular junction becomes less stable due to morphological changes in the alpha motor neurons caused by oxidative stress, neurodegeneration, and inflammation (for a review, see Deschenes, 2011). These events affect neurotransmitter release and muscle activation and alter the normal cycle of denervation and reinnervation over the lifespan, resulting in fewer but larger surviving motor units and muscle fiber loss. Importantly, loss of muscle fiber innervation is thought to be a major cause of sarcopenia, an age-related disorder associated with loss of muscle mass and function (for reviews, see Hunter et al., 2016; Pascual-Fernández et al., 2020; Verschueren et al., 2022). With aging, there is also a loss of muscle fiber cross-sectional area, increased atrophy of type II fibers compared to type I fibers (Lexell et al., 1988), and slower contractile velocity (Larsson et al., 1997). The rate of muscle relaxation has also been reported to slow with aging (Callahan & Kent-Braun, 2011; Molenaar et al., 2013), likely due to slower cross-bridge mechanics and lower rates of Ca^{2+} uptake into the sarcoplasmic reticulum (Hunter et al., 1999). However, these measures vary between individuals and are influenced by, for example, gender and exercise habits (Hunter et al., 1999; Molenaar et al., 2013).

2.4.3   Exercise and the aging brain

Regular exercise and PA have been consistently associated with better cognitive function from early to late life (for reviews, see Erickson et al., 2015, 2019; Hillman et al., 2008; Iso-Markku et al., 2024). In addition, aerobic and strength training interventions have shown improvements in measures of cognitive function (for reviews, see Northey et al., 2018; P. J. Smith et al., 2010). These benefits of exercise are likely due to improvements in brain function and structure. Exercise has been shown to promote neuronal differentiation, survival, and plasticity by increasing neurovascular function and neurotransmitter levels, and stimulating the production of growth factors, such as brain-derived neurotrophic factor (BDNF)

and insulin-like growth factor-1 (IGF-1) (for a review, see Vecchio et al., 2018). Aerobic and strength training, aerobic fitness, and PA have all been associated with larger gray and white matter volumes in several brain regions throughout the life span (Burzynska et al., 2014; Colcombe et al., 2003, 2006; Erickson et al., 2009, 2011; Fontes et al., 2017; Oh et al., 2023; Ruotsalainen et al., 2019). A growing body of literature also suggests that aerobic fitness, PA, and exercise training are associated with functional connectivity between a wide variety of brain regions and subcortical structures (for a review, see Moore et al., 2022).

The effects of exercise on the aging brain are also reflected in a few ERP components related to cognition. The relationship between exercise and the P3b component is especially well studied. A recent systematic review by Pedroso et al. (2017) disclosed positive associations of both PA background and exercise training interventions with larger P3b amplitude, with minor evidence for shorter P3b latency in older individuals. Of the PA studies, six out of nine showed beneficial effects on P3 amplitude, although the method of determining PA levels varied between studies. The included exercise intervention studies also varied in training methods, such as aerobic exercise, dance, and Tai Chi (Pedroso et al., 2017). Similar results have been reported in the systematic review by Kao et al. (2019) for both physical activity and cardiorespiratory fitness. To my knowledge, only two studies have examined the effects of strength training on the P3b component. In the study by Tsai et al. (2015), decreased P3b amplitudes were found after 12 months of follow-up in a control group of older men, while the intervention group had no change in amplitudes after 12 months of strength training. They also found an increase in IGF-1 levels and a correlation between P3b amplitude and IGF-1 level change in the strength-trained group. A study by Özkaya et al. (2005) found an increase in peak-to-peak N2-P3 amplitudes in the strength training group after nine weeks of training. However, they found that this improvement occurred only at the frontal electrode site. Overall, long-term studies of the association between the P3 component and strength training are lacking.

2.5 Menopausal transition

Menopause is the permanent cessation of ovarian reproductive function, either spontaneous (natural menopause) or iatrogenic (secondary menopause), and it is an inevitable component of female aging (Davis et al., 2015). Menopause is defined as the final menstrual period, which is followed by 12 months of amenorrhea (Harlow et al., 2012). The mean age for natural menopause is 48.8 years worldwide, but this varies by geographic region and is higher in wealthier countries (for a review, see Schoenaker et al., 2014). In a 2007 study sample, the median age of menopause in Finland was 51 years (Pakarinen et al., 2010).

The menopausal transition, or perimenopause, is usually defined as the time between the onset of irregular menstrual cycles and menopause and is characterized by dramatic changes in the hypothalamic-pituitary-ovarian (HPO)

axis function (Talaulikar, 2022). The duration of the perimenopausal phase is largely variable and influenced by the age at which it begins, for example, the median duration ranged from approximately 4 to 9 years from the oldest to the youngest quartile of age at onset, respectively, in a recent study from the United States (Paramsothy et al., 2017). According to the 'The Stages of Reproductive Aging Workshop +10 (STRAW+10)' criteria (Harlow et al., 2012), perimenopause is further divided into two phases, early and late perimenopause, based on menstrual patterns and endocrine levels. *Early perimenopause* is characterized by increased variability in menstrual cycle length, defined as a persistent difference of 7 or more days from the usual menstrual cycle length within 10 consecutive cycles. It is accompanied by elevated but variable follicle-stimulating hormone (FSH) levels in the early follicular phase and low antral follicle count (AFC) and anti-Müllerian hormone (AMH) levels. *Late perimenopause* is characterized by the occurrence of amenorrhea for 60 days or longer and FSH levels above 25 IU/L, although some fluctuation may still occur (Harlow et al., 2012). Perimenopause is also characterized by a decrease in estradiol (E2) levels, especially in the late phase. However, it fluctuates highly (to even higher values than in premenopause) until menopause, while FSH has shown a more consistent increase. Importantly, other hormonal changes also occur, including decreases in progesterone and inhibin B levels and increases in luteinizing hormone levels (Davis et al., 2015; Santoro et al., 2008, 2021; Talaulikar, 2022). The changes in hormone levels throughout the menopausal transition are associated with progressively anovulatory menstrual cycles until final menopause (Talaulikar, 2022).

Approximately 80% of women experience symptoms during perimenopause, such as vasomotor symptoms (hot flashes and night sweats), sleep disturbances, anxiety, depression, pain, bone loss, and cognitive dysfunction (Greenblum et al., 2013, for reviews, see Brinton et al., 2015; Santoro et al., 2021). Although some symptoms are pronounced in early post-menopause, there is evidence of pronounced symptoms, such as cognitive decline, particularly during the menopausal transition (Greendale et al., 2009; Maki et al., 2021; for a review, see Metcalf et al., 2023), although there are also conflicting findings (Karlamangla et al., 2017; Luetters et al., 2007; Meyer et al., 2003). Interestingly, Greendale et al. (2009) found a cognitive deficit in the late perimenopausal stage and a return to baseline after menopause. Tirkkonen et al. (2022) also found a connection between cognitive and walking performances especially in late perimenopausal women, while no association was found in early perimenopause or postmenopause. They also found improvements in cognitive functions at follow-up measurements after menopause, especially in the late perimenopausal group, which may indicate a cognitive deficit in the late perimenopausal stage. Many perimenopausal symptoms are mainly neurological and highlight the effect of hormonal fluctuations during menopausal transition on the nervous system function (Brinton et al., 2015).

2.5.1 Menopause and motor function

The changes in hormonal levels during menopause have been demonstrated to expose women to an early decline in motor function and muscular performance (Bondarev et al., 2018; Sipilä et al., 2020; Sipilä & Poutamo, 2003). This is due to a loss of muscle mass and strength, which increases the risk of sarcopenia in postmenopausal women (Sipilä et al., 2020). A study by Bondarev et al. (2018) demonstrated a decline in handgrip strength and lower body power production in postmenopausal women compared to premenopausal women. In perimenopausal women, there was already a decline in jumping height, although this was relatively subtle. Menopause has been linked to various changes in muscle force generation properties in hormone replacement therapy (HRT) studies, indicating an association between the reduction in hormones and muscle contractile mechanisms (Finni et al., 2011; Qaisar et al., 2013; Ronkainen et al., 2010).

2.5.2 Hormonal effects on neuromuscular mechanisms

Female sex hormones have been shown to have both facilitative and suppressive effects on neurotransmitter systems. Estrogen has a facilitating effect on the excitatory neurotransmitter, glutamate transmission, and suppresses the inhibitory neurotransmitter, GABA input. In contrast, progesterone facilitates GABAergic transmission, mainly through $GABA_A$ receptors, and suppresses glutamate response. The effects of female hormonal levels on motor cortical excitatory and inhibitory mechanisms have been studied with somewhat mixed results. Inghilleri et al. (2004) found an alteration in cortical excitability due to hormonal changes during the early follicular phase, specifically a decrease in MEP facilitation after repetitive TMS on day 1 of the menstrual cycle. Their findings are consistent with the evidence that estrogen enhances glutamate neurotransmission and decreases GABAergic inhibition. They did not find any modulation of SP duration after repetitive TMS between day 1 and day 14 of the cycle. On the other hand, M. J. Smith et al. (1999, 2002) reported increased intracortical inhibition (ICI) after paired-pulse TMS in women in the luteal phase compared to the mid-follicular and late follicular phases. This finding is consistent with previous evidence of progesterone's facilitatory effect on GABA, specifically $GABA_A$-mediated inhibition. In contrast, Hattemer et al. (2007) investigated both ICI and SP as well as intracortical facilitation (ICF) using paired-pulse TMS in women with ovulatory and anovulatory cycles and found no significant differences in ICI, ICF, or SP across four different cycle days in women with ovulatory cycles. However, they did find increased inhibition in anovulatory women during menstruation, which was explained by estrogen withdrawal at this stage of the cycle, although results in ovulatory women did not indicate a similar relationship. Interestingly, Hausmann et al. (2006) found no difference in MT or SP in women between different cycle days. However, they found a reduced ipsilateral SP in the late follicular phase and a negative association between ipsilateral SP duration and estrogen and progesterone. The

authors discussed that the effect of progesterone on transcallosal inhibition is likely due to its neuromodulatory effects on glutamatergic transcallosal fibers, but this remains speculative, as the mechanisms of ipsilateral SP are not yet fully understood.

Force potentiation is a phenomenon in skeletal muscle in which recent muscle activity temporarily increases the force produced (Vandenboom, 2009). It is often recorded as an increase in isometric twitch force by evoked non-voluntary stimuli measured before and after a conditioning contraction (Hamada et al., 2000; Miller, Herda, Trevino, Sterczala, & Ciccone, 2017). This effect is referred to in the literature as post-activation potentiation or twitch potentiation (Hamada et al., 2000; Miller, Herda, Trevino, Sterczala, & Ciccone, 2017; for reviews, see Hodgson et al., 2005; D. G. Sale, 2002). The mechanism of potentiation is proposed to involve phosphorylation of myosin regulatory light chains (pRLC), which makes actin and myosin more sensitive to Ca^{2+} release from the sarcoplasmic reticulum and alters the structure of the myosin head, leading to an increase in the rate at which myosin cross-bridges move from a non-force-generating state to a force-generating state (Hodgson et al., 2005). The magnitude of the measured potentiation is dependent on the intensity and duration of the conditioning contraction and muscle fiber type (Fukutani et al., 2014; Hamada et al., 2000). Twitch force potentiation is shown to be lower in older adults than young adults and interestingly, already in women aged 45-54, which is about the same as the average age for menopause (Kuu et al., 2007; Miller, Herda, Trevino, Sterczala, Ciccone, & Nicoll, 2017). Estradiol has been previously connected to modulation in force potentiation mechanisms and myosin pRLC in mice (Lai et al., 2016). Furthermore, higher twitch torque has been reported in estrogen-containing hormone replacement therapy (HRT) using postmenopausal women compared to their monozygotic co-twins who had never used HRT, suggesting that there is modulation in involuntary force generation mechanisms due to lower estrogen levels in postmenopausal women. However, the association between force potentiation mechanisms and menopause has not been studied.

3 AIMS OF THE STUDY

The main purpose of this dissertation was to investigate the effects of aging and hormonal aging on somatosensory brain function and peripheral neural processing. Specifically, the goal was to examine the effects of aging on cortical somatosensory processing, which may underlie changes in cognitive function. Furthermore, this study aimed to evaluate the effects of a long-term strength training background on sensory-cognitive cortical processing in aging. The final aim of this dissertation was to investigate whether the changes in somatosensory functions are already present in middle-aged women and whether the stage of menopausal transition is associated with excitatory and inhibitory neural mechanisms in the motor cortex and peripheral neural system. This dissertation consists of three original studies.

The specific research questions for each study were as follows:

I   Are neuromuscular inhibitory and excitatory mechanisms, specifically TMS-induced SP and MEP and twitch force potentiation induced by peripheral electric stimulation, modulated in middle-aged women in early and late perimenopausal stages? (*Study I*)

II   Is there a difference in P3m brain responses associated with change detection and updating sensory working memory in older men with different strength training backgrounds? (*Study II*)

III   Do young, middle-aged, and older women differ in attended and non-attended somatosensory brain responses related to sensory gating, change detection, and updating the working memory? (*Study III*)

4   METHODS

4.1   Study designs and participants

Data from three different larger research projects were used in this dissertation: the Estrogenic Regulation of Muscle Apoptosis (ERMA) project (*Study I*) and the SARCOPENIA project (*Study II*), which were conducted at the Faculty of Sport and Health Sciences, University of Jyväskylä, and the Aging brain -study (*Study III*), which was conducted at the Department of Psychology, University of Jyväskylä. A summary of the included studies is presented in Table 1.

TABLE 1   Summary of the studies included in the thesis.

Study	Design	Participants	Brain imaging/ stimulation technique	Tasks	Primary outcomes	Secondary outcomes
I	Cross-sectional	25 early perimeno-pausal women, 38 late perimenopausal women	TMS	Plantar flexion 20, 40, & 60 % MVC, Tibial nerve electrical stimulation, Maximal dorsiflexion	SP duration, MEP amplitude, Twitch force potentiation	E2, FSH, MVC dorsiflexion, MVC plantarflexion, Knee extension strength, Vertical jumping height
II	Cross-sectional	9 older men with a strength training background, 8 older men without a strength training background	MEG	Active somatosensory oddball paradigm: electrical stimulation to the right foot	Deviant P3m (P3), Deviant M200	N/A
III	Cross-sectional	15 young women, 7 middle-aged women, 15 older women	MEG	Passive and active somatosensory oddball paradigm: electrical stimulation to the left hand	Standard M50 & M100 (Active & Passive), Deviant M190 (sMMR), M250 (Passive), Deviant M200, M350 (P3; Active)	Cognitive test battery

E2 = Estradiol, FSH = Follicle-stimulating hormone, MEG = Magnetoencephalography, MEP = Motor evoked potential, MVC = Maximum voluntary contraction, sMMR = Somatosensory mismatch response, SP = Silent period, TMS = Transcranial magnetic stimulation.

4.1.1 Study I

Participants in *Study I* were 63 women aged 48–55 (mean 51.4) years, 25 of whom were early perimenopausal and 38 of whom were late perimenopausal (Table 3). They were part of the core-ERMA subgroup of the study population of the ERMA project organized at the Gerontology Research Center (GEREC) and the Faculty of Sport and Health Sciences at the University of Jyväskylä (Kovanen et al., 2018). The ERMA study population was initially selected from the Finnish National Registry, maintained by the Population Register Centre. Initially, 6878 women aged 47-55 living in the Jyväskylä area were randomly chosen to receive an invitation letter with a pre-questionnaire and general consent, and 46,9 % responded. Women who consented and met the inclusion criteria (n=1627) were invited to a laboratory visit, where a structured health interview was conducted, their fasting blood samples were taken, and they filled out an informed consent form for the full ERMA study protocol. If a participant reported any serious or unclear health problems, they were examined by a physician to ensure safe participation in the physical performance tests. They also kept a menstrual diary for at least 12 weeks. Exclusion criteria included estrogen-containing hormonal preparations or other medications that affect ovarian function, current pregnancy or lactation, conditions affecting ovarian function, including bilateral oophorectomy, body mass index (BMI) > 35 kg/m^2 (based on self-reported height and weight), and chronic diseases or medications that seriously affect muscle function.

Each participant's FSH level was measured from a blood sample taken during the first five days of the menstrual cycle, if possible, and from a menstrual diary kept for six to twelve months to determine the participant's menopausal status. Each participant's E2 levels were also measured. FSH and E2 were measured by immunoassay using the IMMULITE 2000 XPi (Siemens Healthcare Diagnostics, UK). The core-ERMA group used in the current study consisted of perimenopausal women who had an intact uterus and who were not currently using or had not used any hormonal contraception or other medication that could interfere with the tracking of their menstrual bleeding pattern in the previous three months. Perimenopausal status was further defined according to the Stages of Reproductive Aging Workshop guidelines (Harlow et al., 2012). Participants with FSH less than 25 IU/L and irregular menstrual cycles were defined as *early perimenopausal* (EP), and those with FSH greater than 25 IU/L were defined as *late perimenopausal* (LP). Women with FSH above 30 IU/L and no menstrual bleeding in the past three to six months were considered postmenopausal, and women with FSH below 17 IU/L and reporting regular menstrual bleeding were considered premenopausal and were therefore excluded from the current study. Women who were defined as perimenopausal and having a natural hormonal cycle were invited to participate in a subset of functional testing, of which 91 volunteered to participate. The researchers who performed the measurements and data analysis were blinded to the participant's menopausal status and other background information. Good-quality electrophysiological data were obtained from 63 participants and were therefore included in the present study. Table 2

shows the perimenopausal stage characteristics, i.e. the measured hormonal levels and menstrual bleeding patterns reported over three months for the included participants. See the characteristics of the participants in Table 3.

TABLE 2   Perimenopausal stage characteristics in *Study I*.

	Early perimenopausal (n=25)	Late perimenopausal (n=38)
FSH (IU/l)	17.32 ± 4.79***	48.25 ± 22.28***
E2 (nmol/l)	0.374 ± 0.257*	0.249 ± 0.200*
Mean cycle length (d)	36.8 ± 22.2[a]***	65.8 ± 41.7[b]***
Mean bleeding days	6.0 ± 1.4[a]	5.3 ± 1.5[b]
Mean non-bleeding days	34.7 ± 31.6[a]**	65.2 ± 49.1[b]**

Data presented as means and standard deviations.
P-values tested with independent samples t-test.
*p<.05, **p<0.1, ***p<.001, [a]n = 23, [b]n = 34.
E2 = Estradiol, FSH = follicle-stimulating hormone, IU/L = international units per liter, nmol/L = nanomoles per liter.

4.1.2 Study II

Participants in *Study II* were nine men (76 to 82 years) with a ten-year strength training background and eight men (74 to 80 years) without a strength training background (Table 3). This study was performed as an ancillary study of a larger SARCOPENIA project, a randomized trial started in 2007 at the University of Jyväskylä, Faculty of Sport and Health Sciences (Ahtiainen et al., 2015). Initially, participants were recruited for the project through an advertisement in a local newspaper, targeting older men of about 70 years of age. All volunteers underwent a detailed medical screening and participants who passed the physical examination were included in the study. Exclusion criteria were cardiovascular and pulmonary disease, malfunctions of the thyroid gland, diabetes, obesity (BMI ≥ 30), or any other disease or medication that might have interfered with the ability to perform exercise training and testing. Participation in systematic exercise training in the previous year was also an exclusion criterion. After medical screening, at that time, a total of 35 men participated in a one-year supervised intervention study with three strength training groups, differing only in muscle biopsy measurements, and a control group with no training intervention. After baseline measurements, block randomization was performed using a random number generator to assign participants to the strength training and control groups (3:1 for exercise and control, but 1:1:1:1 for each initial group). Twenty-six participants were randomly assigned to the three exercise groups with identical strength training interventions and nine to the non-exercise control group.

During the first year of the SARCOPENIA project, the exercise group participated in a year-long supervised strength training intervention (twice a week for the first six months and then three times a week for six months) at the university gym. The strength training exercises included leg presses, squats, and

knee extensions and flexions for the lower limb muscles, together with four to five exercises to target the other major muscles of the body. The training was initially done with light loads, seven to eight exercises at 40–60% of one repetition maximum (1RM) with three 10–20RM sets and short rest periods in between. After one month, the loads were gradually increased to 60–80% of 1RM, three to five sets of 8–12RM per set, aiming to increase muscle mass. After three months, the number of exercises was increased to nine or ten, and the training program was incorporated with higher loads, 70–90% of 1RM, with longer recovery periods, using 5–10RM sets to optimize improvement in maximal strength. The training program also included two sets of lower loads, 40–50% of 1RM for 8–12 repetitions, with higher movement velocities to enhance muscle power (Ahtiainen et al., 2015). During the supervised strength training period, participants kept a training diary.

After the one-year intervention, participants in the exercise group continued voluntary, unsupervised strength training approximately 2 times per week. The participants in the control group continued with their typical daily routines, abstaining from strength training. Follow-up strength measurements were taken after the first and second years of voluntary training, and later at four and seven years. Participants also completed questionnaires at each follow-up measurement. During the first year of the study, three participants in the exercise group were unwilling to continue with the study program and one participant died. Later, two participants in the exercise group and one in the control group withdrew from the study. In addition, two participants in the control group moved to another region, one participant could not be reached, and one participant died. One participant in the exercise group discontinued strength training after the first year of intervention and voluntarily switched to the control group. Twenty-four men attended the ten-year follow-up and were invited to participate in this ancillary study. After additional screening, six participants in the exercise group and one participant in the control group were excluded from MEG registration because of a diagnosis of neurological or psychiatric disease, such as Parkinson's disease, Alzheimer's disease, or depression. One participant in the exercise group could not be measured due to dental fillings, one was not measured due to musculoskeletal problems, and one could not be contacted.

Finally, 14 participants from the original study population participated in the present MEG recordings, 10 of whom were part of the original exercise group and had continued self-directed strength training until the ten-year follow-up. Mean ± SD training adherence during the first year was 93 ± 8%, and participants reported 2.2 ± 0.4 strength training sessions per week during subsequent follow-up. One participant was later excluded from the exercise group due to insufficient MEG data (n = 9). The control group of the present study consisted of four original participants and four additional recruits (n = 8). Inclusion criteria for the recruits were age 72–80 years, no history of strength training or other regularly performed moderate or vigorous exercise, no neurological or psychiatric diseases or medications affecting the nervous system or diseases that prevent normal exercise training or daily activities, and no pacemaker or metal

implants that prevent MEG recording. All original participants, except one in the exercise group and one in the control group, reported doing endurance-type physical activities (such as skiing, swimming, and walking) during the ten years. Participants in the exercise group reported that they remained in good health and were able to continue with their strength training regimen during the follow-up period. One participant reported a musculoskeletal condition that did not interfere with exercise training. All control participants reported health-related changes during the follow-up period that did not prevent them from participating in the MEG recordings. All recordings and analyses were performed in a blinded manner concerning the participants' group status. All participants reported being right-handed. See the characteristics of the participants in Table 3.

4.1.3 Study III

Study III sample consisted of 15 young adults (20 to 28 years), 7 middle-aged adults (46 to 56 years), and 15 older adults (64 to 78 years; Table 3). Initially, the participants were recruited to take part in the study at the University of Jyväskylä, Department of Psychology, via email lists at the University of Jyväskylä and the University of the Third Age (an open university in Jyväskylä for older adults interested in science). Inclusion criteria were female gender, right-handedness, good general health, and age of 18–30, 45–60, or 64–80 years. The female gender was chosen because of the difficulty in recruiting male volunteers and to make the groups comparable. Exclusion criteria were pregnancy or lactation, diagnosed neurological or psychiatric disease, medications affecting the central nervous system, previous brain surgery, drug or alcohol addiction, any sensory deficits (except vision corrected with glasses), speech disorders, dyslexia or attention deficit disorder, acute life crisis or stressful life situation, and any metal implants or braces that prevented participation in the MEG recordings. After the recruitment process, 22 young, 11 middle-aged, and 15 older adults volunteered originally for the study and participated in the MEG measurements and cognitive tests. The sample size was estimated based on previous studies using somatosensory stimulation and paradigms similar to *Study III* in young (Xu et al., 2021) and older adults (Strömmer et al., 2014). During the first visits, participants completed questionnaires on their health status, education, PA habits (hours/week, months/year), and the Beck Depression Inventory-II (BDI-II). A Mini-Mental State Examination (MMSE) was administered to older adults. Later, data from five participants were excluded due to technical difficulties during MEG recording and from six participants due to bad MEG signal. See the characteristics of the participants in Table 3.

TABLE 3 Background characteristics of the participants from different datasets used in this thesis.

	Study I		Study II		Study III		
	Early peri-menopausal (n=25)	Late perimen-opausal (n=38)	Exercise group (n=9)	Control group (n=8)	Young adults (n=15)	Middle-aged adults (n=7)	Older adults (n=15)
Age, y	51.0 ± 2.0	51.6 ± 1.8	77.7 ± 2.1	77.5 ± 2.5	23.4 ± 2.2	52.4 ± 3.5	69.1 ± 4.2
Height, cm	163.8 ± 0.1	164.2 ± 0.1	174.0 ± 3.6	173.3 ± 8.4	164.7 ± 4.3 (n = 14)	168.1 ± 4.8	161.5 ± 5.4 (n = 11)
BMI[a]/Weight[b] (kg)	25.4 ± 4.4 [a]	25.3 ± 3.7 [a]	80.1 ± 10.6 [b]	78.3 ± 8.9 [b]	61.0 ± 7.3 [b] (n = 13)	75.1 ± 18.1 [b]	62.2 ± 8.5 [b] (n = 10)
PA habits, n (%)							
Low activity[c]/ 0-2 h per week[d]	4 (16) [c]	6 (16) [c]	0 (0) [d]	5 (62.5) [d]	4 (28.5) [d]	3 (43) [d]	4 (29) [d]
Moderate activity[c]/ 2-4 h per week[d]	7 (28) [c]	7 (18) [c]	5 (56) [d]	2 (25) [d]	6 (43) [d]	3 (43) [d]	4 (29) [d]
High activity[c]/over 4 h per week[d]	14 (56) [c]	25 (66) [c]	4 (44) [d]	1 (12.5) [d]	4 (28.5) [d]	1 (14) [d]	6 (43) [d]

Data are presented as means and standard deviations unless otherwise noted. BMI = body mass index, PA = Physical activity, SD = standard deviation.

4.2 Assessment of functional and cognitive abilities

4.2.1 Functional measurements

In *Study I*, the current PA level of participants was assessed using the seven-point scale for the current level of weekly leisure-time PA questionnaire (Hirvensalo et al., 1998). The questionnaire consisted of seven response categories: (0) inactive, (1) light activity 1 to 2 times per week, (2) light activity several times per week, (3) moderate activity 1 to 2 times per week, (4) moderate activity several times per week, (5) vigorous activity several times per week, and (6) competitive sports and related training several times per week. This scale has recently been shown to correlate well with accelerometer-based PA and mobility variables (Hyvärinen et al., 2019). Categories 0 and 1 were combined into the low-activity group, 2 and 3 into the moderate-activity group, and 4, 5, and 6 into the high-activity group.

In *Study III*, the current level of PA was reported within a health questionnaire with a non-standardized question of hours per week used for exercise and PA with five categories: (1) less than 1 hour a week, (2) 1-2 hours per week, (3) 2-3 hours per week, (4) 3-4 hours per week, (5) more than five hours per week. In *Study II*, the participants were asked to report their weekly hours of physical activity during their health interview.

In *Study I*, maximal isometric knee extension strength was measured in Newton meters (Nm) in one leg on the dominant hand side using a Good Strength dynamometer chair (Metitur Oy, Jyväskylä, Finland). The participant`s knee was positioned at an angle of 60° from full extension and the ankle was strapped to a force transducer. The participant was instructed to extend the knee with maximum force and verbal encouragement. The best performance of three to five isometric extensions was selected for the analysis.

In *Study I*, vertical jumping height was measured three to five times using a contact mat. Jump height indicates the participant's ability to elevate the body's center of gravity during a vertical countermovement jump (Bosco et al., 1983). The flight time (t) was measured, and the vertical jumping height (m) was calculated as follows:

$$\frac{g \times t^2}{8} \times 100^{25}$$

The highest value obtained from three to five jumps was selected for analysis.

4.2.2 Cognitive tests

In *Study I*, a neuropsychological test battery consisting of the following eight tests was used to assess the cognitive abilities of the participants: the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 2012, p. 471), the Rey-Osterrieth Complex Figure Test (ROCF; Brauer Boone, 2000), the Logical Memory Task (Lezak, 2012, p. 490), the Trail Making Test A and B (TMT-A; TMT-B; Bowie & Harvey, 2006), the Stroop Color-Word Test (Alvarez & Emory, 2006), the Digit Span Task (Ramsay & Reynolds, 1995) both forwards and backwards, the Letter-Number

Sequencing task (LNS; Crowe, 2000) and the Verbal Fluency Test, a version of the Controlled Oral Word Association (Lezak, 2012, p. 694). In addition, the Finger Tapping task (Ruff & Parker, 1993), and the Handgrip strength test were used to assess upper extremity motor skills and strength. The test battery was administered by a psychologist or a trained psychology student to all participants in the same order. The tests were scheduled within approximately one week of participation in the MEG measurements and the duration of the entire test battery was approximately 1–1.5 h per participant.

4.3 Data recording, preprocessing, and analysis

4.3.1 Transcranial magnetic stimulation and force potentiation recordings and analysis in *Study I*

4.3.1.1 Neuromuscular measurements

The stimulation recordings were performed on the right leg with the participant seated on an ankle dynamometer chair, custom-made at the University of Jyväskylä (Peltonen et al., 2010). Their right knee was extended to 180º, and their foot was strapped to the footplate at an angle of 90º, with the back and head resting against the backrest. Two surface electrodes (Ambu® BlueSensor N, 22 × 28 mm, Ballerup, DK) were placed on the tibialis anterior and medial gastrocnemius muscles for bipolar EMG recording with a 20 mm inter-electrode distance. The ground electrode was placed proximally.

Maximum voluntary contraction (MVC) torque for right ankle dorsiflexion was determined before TMS application. MVC was defined as the highest torque of two maximal dorsiflexion contractions and the values of 20%, 40%, and 60% of MVC were calculated. TMS was performed with the Magstim Rapid stimulator (Magstim, Whitland, UK) using a double 70 mm coil (figure-of-eight coil). Single pulse stimulation was applied on the motor cortex over the measured and marked center of the scalp, with a 45° angle from the mid-sagittal plane to target the lower limb representation area on the contralateral hemisphere. The stimulation intensity was gradually increased to find the optimal stimulation location (hotspot) and to assess the RMT. As the stimulation of lower limb muscles can be challenging, especially without navigated TMS, the RMT for the lower limb was set at the occurrence of three visible MEPs of at least 50 µV in relaxed tibialis anterior. As the lower limb representation area of the MI is situated inside the longitudinal fissure and may require a relatively high stimulus intensity to elicit MEPs, we recorded the stimulator output used for each participant to control for possible effects of stimulation intensity. Participants were instructed to perform isometric dorsiflexion at 20%, 40%, and 60% of their MVC, with rest periods in between. Such submaximal force levels are recommended (Säisänen, Pirinen, et al., 2008), as they are relatively easy to maintain during the measurement. The produced force and the target force level

were displayed on the screen in front of the participants. The contraction was maintained continuously at the target level while 6 to 10 stimulations were delivered at the individual hotspot with approximately 10-second ISIs.

To record twitch force potentiation, peripheral electrical stimulation was applied to the tibial nerve in the popliteal fossa. The initial determination of the optimal stimulation point was conducted with the participant in the prone position. By gradually increasing the stimulation intensity, the optimal location and intensity were defined when the peak-to-peak amplitude of the M-wave in the medial gastrocnemius muscle and the configuration of the M-wave could be repeated at least three times. The cathode electrode (Ambu® WhiteSensor 4500 M, 79 mm, Ballerup, DK) was placed at this site and the anode electrode (V-trodes; Mettler Electronics, Anaheim, CA, USA) was placed slightly proximal to the patellofemoral joint. Supramaximal electrical stimulation at 150% intensity of the individual maximum M-wave of 1 ms duration was delivered with a constant current stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK), while the participant was seated in the dynamometer chair. The participant was seated in a relaxed position as the first stimulus was delivered. After the first stimulus, the participant was instructed to perform a maximal isometric plantarflexion during which the second stimulus was delivered. After 2–5 s of relaxation, the third stimulus was delivered to a relaxed muscle. Participants received visual feedback on their torque level on the screen in front of them and verbal encouragement to perform the maximal contraction. Three trials with three stimulations were performed with a rest period of 60 seconds between each trial. EMG signals were amplified 1000-fold and band-pass filtered (10 Hz–1 kHz). The ankle MVCs were measured with a torque transducer (Kistler Group, Switzerland) mounted between the ergometer servomotor and the foot platform.

4.3.1.2   Data analysis

Individual TMS data were analyzed manually using Spike2 software (version 6.17, Cambridge Electronics Design, Cambridge, UK). MEP onset was taken as the point at which the EMG signal for the tibialis anterior muscle exceeded baseline activity, and the MEP end as the point at which the complete EMG silence began. The same time point was also recorded as the SP onset. SP end was the point at which baseline EMG activity returned. MEP amplitude was defined as the largest peak-to-peak amplitude. For statistical analysis, both "absolute" SP duration (SP start–SP end) and "relative" SP (MEP start–SP end) were recorded (Säisänen, Pirinen, et al., 2008; Stetkarova et al., 1994). If a participant had four or more successful MEPs and SPs in one force level, those with the shortest and longest durations were not included in further analysis. From the remaining recordings, mean values for SP and MEP were calculated for each participant for each force level.

Electrical stimulation data were analyzed using Matlab (R2015a, 8.5.0, Mathworks Inc., Natick, MA, USA). Peak twitch torque (PTT) and MVC torque were determined manually from the torque signal. Twitch force potentiation was analyzed by comparing the PTT of the pre-MVC twitch peak amplitude to the

post-MVC twitch peak amplitude in the three recorded trials using the following equation:

$$Potentiation\ (\%) = \left(\frac{postMVC\ \frac{PTT}{preMVC}\ PTT}{preMVC}\ PTT \right) \times 100$$

The best potentiation effect and the best MVC outcome from the three trials were selected for further analysis.

4.3.2 Magnetoencephalography recordings and analysis in *Studies II* and *III*

4.3.2.1 Stimulations and tasks

In *Studies II* and *III*, a somatosensory oddball task with electrical stimulation was used to study somatosensory processing. In *Study II*, stimulation was delivered to the hallux and fourth toe of the right foot using two custom-made non-magnetic ring electrodes placed proximally and distally on each toe, with an inter-electrode distance of 1 cm. The stimuli consisted of 500 monophasic electrical pulses of 0.2 ms duration. The ISI was 1000 ms, with a jitter of 2-3 ms. Standard stimuli (p=.9) were delivered to the fourth toe and deviant stimuli (p=.1) to the hallux. Stimulation intensity was individually adjusted at 120–150% of the sensory threshold to a comfortable level with clear sensation without pain, separately for each toe. Participants were instructed to focus on the stimuli and respond to each deviant stimulus by pressing a button in a response box with their left index finger, with their gaze fixed forward on a black dot set approximately 1.5 m in front of them.

In *Study III*, somatosensory electrical pulses with a duration of 0.2 ms were delivered to the participant's left index and little fingers, with a 500 ms stimulus-onset asynchrony. Ring electrodes were placed above the proximal and distal phalanges of both fingers. The stimulus intensity was set at 150% of the individual sensory threshold, which was tested separately for each finger before the experiment. Standard (p=.9) and deviant (p=.1) stimuli were delivered to different fingers. The assignment of the two finger locations as standard and deviant was counterbalanced between two blocks of stimuli. In one block, the deviant stimulus was delivered to the index finger, and the standard stimulus was delivered to the little finger. In the second block, this allocation was reversed. There were 500 stimuli in each block, with a total of 1000 stimuli delivered in the two blocks. Stimuli were presented in a pseudo-random order, with at least two standard stimuli delivered between successive deviant stimuli. Two different conditions were used in the *Study III*. In the passive (non-attended) condition, participants were instructed to ignore all stimuli and focus on a silent movie displayed on a screen placed approximately 1.5 m in front of them. In the active (attended) condition, participants were instructed to focus on the stimuli and to respond to each deviant stimulus by pressing a button in a response box with their right index finger, while keeping their eyes fixated on a cross in the center of the screen. The stimulus presentation was controlled by the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, United States).

Mean stimulus intensities were 2.3 ± 0.6 mA and 2.0 ± 0.6 mA for young adults, 3.1 ± 0.8 mA and 2.6 ± 0.3 mA for middle-aged adults, and 3.9 ± 1.4 mA and 3.2 ± 0.8 mA for older adults for the index and little fingers, respectively. Stimulus intensities for both fingers were significantly higher for older adults than for young adults (index finger: p<.001, mean difference 1.6 mA, and little finger: p<.001, mean difference 1.1 mA), which is a common finding for electrical thresholds in older adults (Kemp et al., 2014).

4.3.2.2   Magnetoencephalographic data registration

Somatosensory evoked field recordings for *Studies II* and *III* were performed with a 306-sensor MEG device (Elekta Neuromag®, Triux™, Stockholm, Sweden) in a magnetically shielded room with a bandpass of 0.1–330 Hz and a sampling rate of 1000 Hz. To register head shape and position, five continuous current head position indicator (HPI) coils were placed on the skin surface: three on the forehead and two behind the ears. The position of the coils was registered with a 3D digitizer (Fastrak®, Polhemus, Vermont, USA) in addition to the nasion and preauricular points and over 100 additional points around the scalp and nose. Eye movements and blinks were recorded with an electrooculogram (EOG) using surface electrodes placed above and below the right eye (the vertical EOG; *Studies II* and *III*) and on the outer canthi of both eyes (the horizontal EOG; *Study III*). In *Study III*, heartbeats were recorded with an electrocardiogram (ECG) using two electrodes placed on the chest. During the MEG recording, participants were asked to sit still, with their hands resting on the table, one hand ready on the response box (when in use), and to avoid excessive blinking and muscle tension. All data were stored for offline analysis.

4.3.2.3   Data preprocessing

Temporal signal space separation (tSSS; Taulu & Simola, 2006) in Maxfilter software (Elekta Neuromag®, Stockholm, Sweden) was used in both *Studies II* and *III* to reduce extraneous artifacts and to detect unacceptable MEG channels. The data were first analyzed offline using Brainstorm software (Tadel et al., 2011). Data were bandpass filtered at 0.1–40 Hz. Eye blinks for both studies and heartbeat artifacts for *Study III* were detected using signal-space projection (SSP; Uusitalo & Ilmoniemi, 1997). In *Study II*, for a few participants, blinks that exceeded the absolute value of the filtered signal by at least six times the standard deviation (SD) were detected and filtered for excessive blinking. Raw data was manually inspected, and segments with muscle tension artifacts were removed.

In *Study II*, data were segmented into epochs from −100 to 450 ms relative to the stimulus onset, with a baseline correction of −100 to −1 ms. A stimulus delay of 3 ms, identified from stimulus artifacts, was corrected. Deviant epochs and an equivalent number of standard epochs preceding a deviant were averaged separately for each subject. The maximum allowed reaction time for deviant identification was 0.999 s, and only those deviants correctly identified by a button press within this time limit were included in the analysis. The epochs were manually inspected and those with visible artifacts were removed from the

analysis. The minimum number of accepted deviants per individual was 29, and the average number obtained for all participants was 43. One participant from the exercise group was excluded from the subsequent analysis due to an insufficient number of accepted epochs.

Data for *Study III* were segmented into epochs from −100 ms to 500 ms relative to stimulus onset. Deviant epochs for both stimulation blocks and an equivalent number of standard epochs preceding a deviant in each block were averaged separately for each subject. Epochs with EOG traces greater than 200 µV or amplitudes larger than 3000e-13 T/m for gradiometers and 4e-12 T for magnetometers were removed. In the *active condition*, deviants correctly identified with a button press within a reaction time of 1.1 s, were included in the analysis. The remaining epochs were also visually inspected, and epoch processing was continued in MNE Python (Gramfort et al., 2014). Data from participants with distorted data were excluded from further analysis. For the *passive condition*, the final accepted number of participants for each group was 12 young, 7 middle-aged, and 14 older adults. For the *active condition*, the final accepted number of participants for each group was 12 young, 6 middle-aged, and 12 older adults. The minimum number of accepted trials was 48 out of 100 per condition.

4.3.2.4   Group source analysis in *Study II*

In *Study II*, the group source estimates for the P3m brain response were first performed in Brainstorm software (Tadel et al., 2011). The head shape of each participant was matched to a standard anatomical template, ICBM152, as no individual magnetic resonance images (MRI) were available. Noise covariance analysis was computed using empty room recordings taken before each participant's research visit. The source model was performed with overlapping spheres and averaged epochs were used to generate minimum norm estimate current density maps in Brainstorm software. Current density maps were normalized using Z-score transformation and finally spatially smoothed. Based on previous P3 studies (Tarkka & Stokic, 1998; Yamaguchi & Knight, 1992), regions of interest (ROIs) were examined using the Brainstorm scout function. Grand average source maps were created by extracting current source density maps with absolute values and creating grand average source maps for each group. Grand average source maps were used to detect ROIs with maximum amplitude between 320 and 390 ms for the exercise and the control groups. Scouts with 40 vertices were created at the maximum amplitude source for each group, and a matching one was created in the contralateral hemisphere. These were investigated for each participant using the group average scout waveform peak as the temporal cue, resulting in different latencies of the peak amplitudes (324–330 ms for the exercise group, 382–388 ms for the control group). A maximum amplitude using the group-determined time window was detected in each participant's scout waveform to explore common activations and hemispheric differences.

4.3.2.5 Sensor-level analysis in *Study II*

For the sensor-level analysis in *Study II*, only gradiometers were included because they provide the best representation of brain activity below a given sensor. The signals from the 204 gradiometers were combined by calculating the root sum square (RSS; sqrt(grad2^2 + grad3^2)) for each of the 102 gradiometer pairs to control for the sign of the amplitude. In the single-sensor analysis, the obtained gradiometer pair signals were used to locate the sensor with the maximum amplitude between 320 and 390 ms for each participant individually. Peak amplitude and latency were measured. We also recorded the average amplitude within the 320–390 ms time window to measure the average activation, as P3 activity involves larger processes and deeper brain areas that co-activate in this brain response (Wronka et al., 2012).

Information from topographic maps and RSS waveforms with maximum activation was used to create sensor groups to detect activity from a larger cortical area. Because the magnetic field maps showed bilateral temporal activity already in the 200–260 ms time window, we measured both early deviant detection (M200) and P3m. Sensor groups were formed for frontotemporal (P3m), temporal (M200, P3m), and parietal (P3m) cortices for both hemispheres, according to topographic maps. For the M200 response, a time window of 200-260 ms was determined from the grand mean waveforms, and for P3m the previously determined time window of 320-390 ms was used for analysis. M200 was detected from temporal sensor groups, and peak amplitudes and latencies were recorded. For P3m, peak amplitudes, peak latencies, and average amplitudes were measured from temporal, frontotemporal, and parietal sensor groups.

4.3.2.6 Sensor-space analysis in *Study III*

First, we calculated grand average waveforms for the SEF responses for each age group and condition. The grand averages, along with previous literature on somatosensory brain responses (van Dinteren et al., 2014b; Strömmer et al., 2014; Tarkka et al., 1996; Terrasa et al., 2018), were used to define the time windows for further analyses. For both *passive* and *active* conditions, M50 and M100 peaks were identified for early components, and time windows of 30–80 ms and 81–120 ms, respectively, were used to analyze standard and deviant stimuli separately. In the *passive* condition, late somatosensory responses were analyzed in two time windows: M190 in the time window of 121–220 ms, and M250 in the time window of 221–290 ms post-stimulus latency. In the *active* condition, two time windows were also selected: M200 was examined in the time window of 120–270 ms, and M350 in the time window of 271–380 ms post-stimulus latency. Later components were defined and selected based on previous literature on late somatosensory oddball responses – with M190 and M250 corresponding to MMR and P3a for the *passive* condition and M200 and M350 corresponding to N250 and P3b for the *active* condition (Hautasaari et al., 2017, 2019; Kangas et al., 2022; Kekoni et al., 1997; Kida et al., 2003; Naeije et al., 2018; Strömmer et al., 2014, 2017; Tarkka et al., 1996). Later components were analyzed for deviant stimuli, as they were

detected specifically for the deviants in the grand average waveforms. Figure 6 shows the grand average waveforms for specific pairs of gradiometers (root mean square; RMS; *sqrt((grad2² + grad3²)/N))* selected for illustration according to the grand average topographic maps for each time window in the *passive* and *active* conditions for each group.
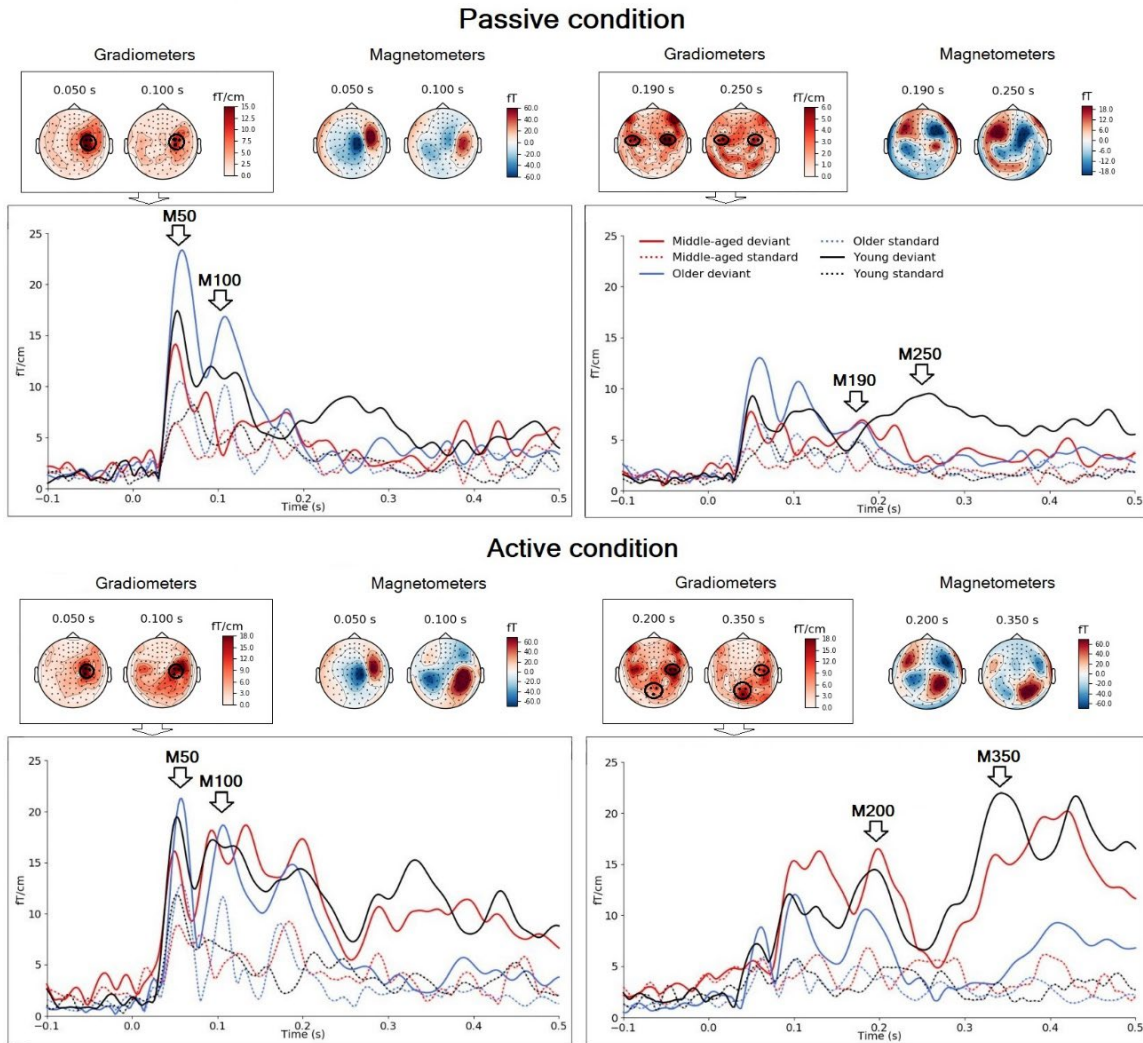
FIGURE 6   Grand average waveforms of selected gradiometer pairs (root mean square) from all participants in passive and active conditions for illustration. Gradiometers were selected for early (M50 and M100) and late (M190, M250, M200, and M350) somatosensory brain responses based on topographic maps.

4.4   Ethical considerations

The study protocol for the complete ERMA study was approved by the Ethics Committee of the Central Finland Health Care District (K-SSHP Dnro 8U/2014), Jyväskylä, Finland. The study protocol for the ancillary study with MEG registrations for the SARCOPENIA project was approved by the Ethics

Committee of the University of Jyväskylä, Jyväskylä, Finland, 10.4.2017. The Aging Brain project was approved by the Ethical Committee of the Central Finland Health Care District. Written informed consent was obtained from all participants in all three studies, and they were informed of their right to withdraw at any time. All three studies were conducted according to the principles of the Declaration of Helsinki.

4.5   Statistical analysis

Statistical analysis for *Study I* was performed using IBM SPSS Statistics version 24 (IBM Corporation, Chicago, IL, USA). Group comparisons between EP and LP women were performed with independent samples t-tests and for the PA variable with the chi-squared test. Variability between stimulation conditions was evaluated with paired samples t-test. Correlations were assessed with Pearson's correlation coefficient or ANOVA. Covariance was assessed with ANCOVA. The significance level was set at p < 0.05.

In *Study II*, statistical analysis was performed using Brainstorm software and IBM SPSS Statistics version 24 (Armonk, NY, USA). The normality of the data was assessed using the Shapiro-Wilk test. All between-group comparisons were assessed with the independent samples t-test for normally distributed data and the Mann-Whitney U test for the non-normal data. Normally distributed data are presented as means and SDs and non-normally distributed data are presented as medians and interquartile ranges (IQRs). P3m and M200 analysis in sensor groups was performed using a linear mixed model (group, hemisphere, group*hemisphere). A large outlier exceeding the upper fence (Q3 + (1.5 * IQR)) was detected in the P3m average amplitude difference scores in the left and right temporal sensor groups. Therefore, we performed an additional analysis, excluding the outlier, as a sensitivity analysis for this variable. Between-group differences in latencies were assessed with the Mann-Whitney U test for non-normally distributed data. P-values (2-tailed) are presented as exact, and the statistical significance threshold was set to <0.05.

In *Study III*, statistical analysis of reaction time and target recognition during the active condition and cognitive test scores were performed using IBM SPSS Statistics version 26 (Armonk, NY, USA). Differences between groups were tested with one-way ANOVA and Bonferroni correction to investigate significant ANOVA results. The alpha level for significant difference was set at <0.05. Statistical analysis for somatosensory brain responses was performed using a spatiotemporal cluster-based permutation test in MNE Python (Gramfort et al., 2013) comparing whole-head spatiotemporal sensor activity based on a two-sample independent t-test. We used the group of young adults as a reference group to compare the responses of middle-aged and older adults separately. This analysis was performed instead of a one-way ANOVA due to the small number of participants in the middle-aged group and the analysis of whole-head activations. Each component was analyzed separately in the selected time

windows described previously. The number of permutations was set to 1,000, and the threshold was set to the equivalent of an F-value of 7 for more localized effects. The alpha level for significant clusters was set at <0.05. Magnetometers and gradiometers were analyzed separately, as magnetometers demonstrated qualitatively different activity. In addition, the M100 component was compared between the active and passive conditions separately within the groups of young adults and older adults, as this response had a similar latency for both conditions. Conditions were compared using a spatiotemporal cluster-based permutation test based on a pairwise t-test. The number of permutations was set to 1,000, and the threshold was set to the equivalent of a t-value of 3 for more localized effects. Magnetometers and gradiometers were analyzed separately, and the alpha level for significant clusters was set at <0.05.

5 SUMMARY OF THE RESULTS

5.1 Neuromuscular inhibitory and excitatory mechanisms modulated in perimenopause in *Study I*

Study I examined the effect of perimenopause on neuromuscular excitatory and inhibitory mechanisms as measured by TMS-induced SP and MEP and electrically induced twitch force potentiation. Results showed that in late perimenopausal women, SP was shorter in 40 % of the MVC condition ($t(61) = 2.473, p = 0.016$) and MEP was larger in 20 % of the MVC condition ($t(61) = 2.511, p = 0.017$; Figure 7). Other force conditions did not show differences between groups in SP or MEP. The difference in SP was also present in relative SP measures ($t(61) = 2.494, p = 0.015$), as were the differences in SP and MEP when controlling for TMS intensities ($F(1,60) = 6.044, p = 0.017$ and $F(1,60) = 7.460, p = 0.008$, respectively). MEP showed a tendency for larger amplitude in early perimenopausal women than in late perimenopausal women in 40 % of the MVC condition, but the difference was not significant ($t(61) = 1.944, p = 0.057$). Both SP duration and MEP amplitude increased with muscle force applied ($p<.01$). Twitch force potentiation did not show group differences, but it was associated with measured FSH levels ($r = -0.262, p = 0.043$). Functional performance did not differ between groups, except for maximum plantar flexion torque ($p = 0.014$), which was lower in late perimenopausal women than in early perimenopausal women (Table 4).
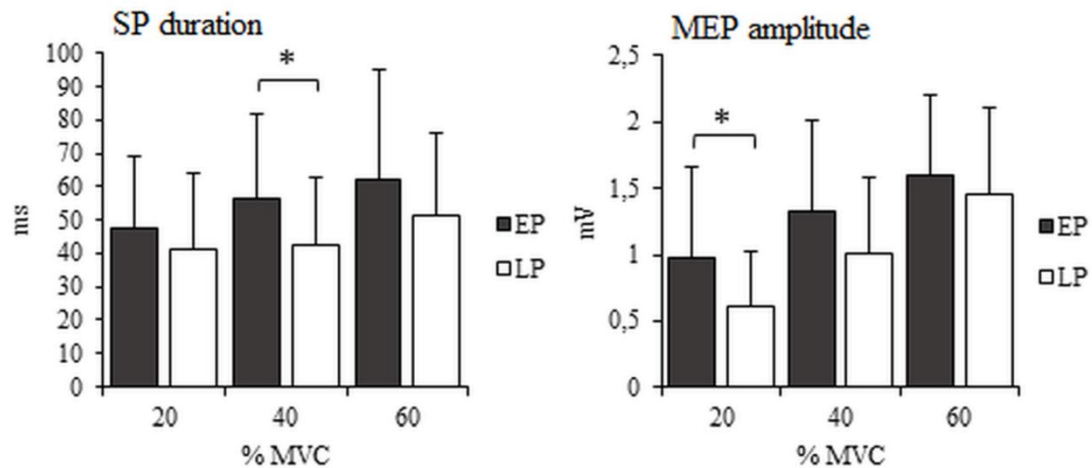
FIGURE 7   Bar graph describing silent period (SP) durations and motor evoked potential (MEP) amplitudes in early perimenopausal (EP) women and late perimeno-pausal (LP) women. Results are shown for 20, 40, and 60 % maximal voluntary contraction (MVC) conditions. Error bars indicate standard deviation. *p<.05.

TABLE 4   Measures of lower limb physical performance and twitch force potentiation.

	Early perimenopausal (n=25)	Late perimenopausal (n=38)	P-value
MVC dorsiflexion (Nm)	31.9 (±9.1)	34.3 (±6.7)	.238
MVC plantar flexion (Nm)	131.1 (±33.9) [a]	108.8 (±32.4) [c]	.014*
Knee extension strength (Nm)	162.2 (±27.9) [a]	153.7 (±38.8) [d]	.360
Vertical jumping height (m)	0.185 (±0.046) [b]	0.200 (±0.037) [e]	.177
Twitch force potentiation (%)	10.1 (±6.3) [b]	6.7 (±9.3) [c]	.124

Data presented as means and standard deviations.
* p<.05
P-values tested with independent samples t-test. MVC = maximal voluntary contraction.
[a]n=23, [b]n=24, [c]n=36, [d]n=35, [e]n=37

5.2 Somatosensory target detection mechanism alters in older strength-trained men in *Study II*

Study II examined the effects of long-term strength training on the cortical processing of the brain during conscious target detection. Results showed no clear differences in peak amplitude, average amplitude, or latency between the exercise and control groups in P3m source analysis or single sensor analysis. The M200 component detected in the temporal sensor groups also showed similar activity between groups. There were no group differences in frontotemporal, parietal, or temporal sensor group peak amplitudes or average amplitudes. However, the control group showed shorter latency in the right temporal sensor

group than the exercise group (U[n9,n8] = 15.5, p = .046). Peak latency was 360 (IQR 335–382) ms in the exercise group and 321 (IQR 320–365) ms in the control group. Because topographic and source activity showed different hemispheric activity patterns between the exercise and control groups, we performed a linear mixed model hemispheric analysis for the sensor group pairs in both hemispheres and both groups. The model showed a difference in P3m hemispheric activity in both peak and average amplitude in the frontotemporal sensor groups (p = .043 and p = .008, respectively), and a group*hemisphere effect in both peak and average P3m amplitude (p = .005 and p = .001, respectively), indicating stronger activity in the right hemisphere for the exercise group and stronger activity in the left hemisphere for the control group. For the parietal sensor groups, there was again a difference in group*hemisphere activity in peak amplitude and average amplitude (p = .013 and p = .019, respectively). Group means and confidence intervals (CI) indicated lower activity in the left hemisphere and stronger activity in the right hemisphere for the exercise group, but similar activity in both hemispheres for the control group. There were no differences between the temporal sensor groups. The mean peak and average amplitudes are shown in Table 5. Grand average waveforms are shown in Figure 8.

TABLE 5   Sensor-group P3m peak and average amplitudes (fT/cm) presented as means and 95% confidence intervals, tested with a linear mixed model for group, hemisphere, and group*hemisphere effects.

Sensor-group	Exercise (n=9)	Control (n=8)	Significant effect
Frontotemporal peak			
Left	35.7 (22.5, 48.9)	50.1 (36.1, 64.1)	Hemisphere,
Right	48.0 (34.8, 61.2)	38.1 (24.1, 52.1)	group*hemisphere
Parietal peak			
Left	38.5 (24.8, 52.2)	48.2 (33.8, 62.9)	
Right	52.9 (39.2, 66.6)	44.5 (30.0, 59.0)	Group*hemisphere
Temporal peak			
Left	46.0 (34.9, 57.0)	43.7 (32.1, 55.5)	
Right	47.6 (36.5, 58.6)	44.9 (33.1, 56.6	
Frontotemporal aver-age			
Left	25.1 (13.3, 36.8)	43.2 (30.9, 55.7)	Hemisphere,
Right	38.2 (26.5, 49.9)	27.8 (15.4, 40.2)	group*hemisphere
Parietal average			
Left	27.8 (15.1, 40.4)	38.6 (25.1, 52.0)	
Right	42.7 (30.0, 55.3)	34.1 (20.7, 47.6)	Group*hemisphere
Temporal average			
Left	36.2 (25.8, 46.6)	35.5 (24.5, 46.6)	
Right	37.8 (27.4, 48.2)	32.9 (22.9, 44.0)	
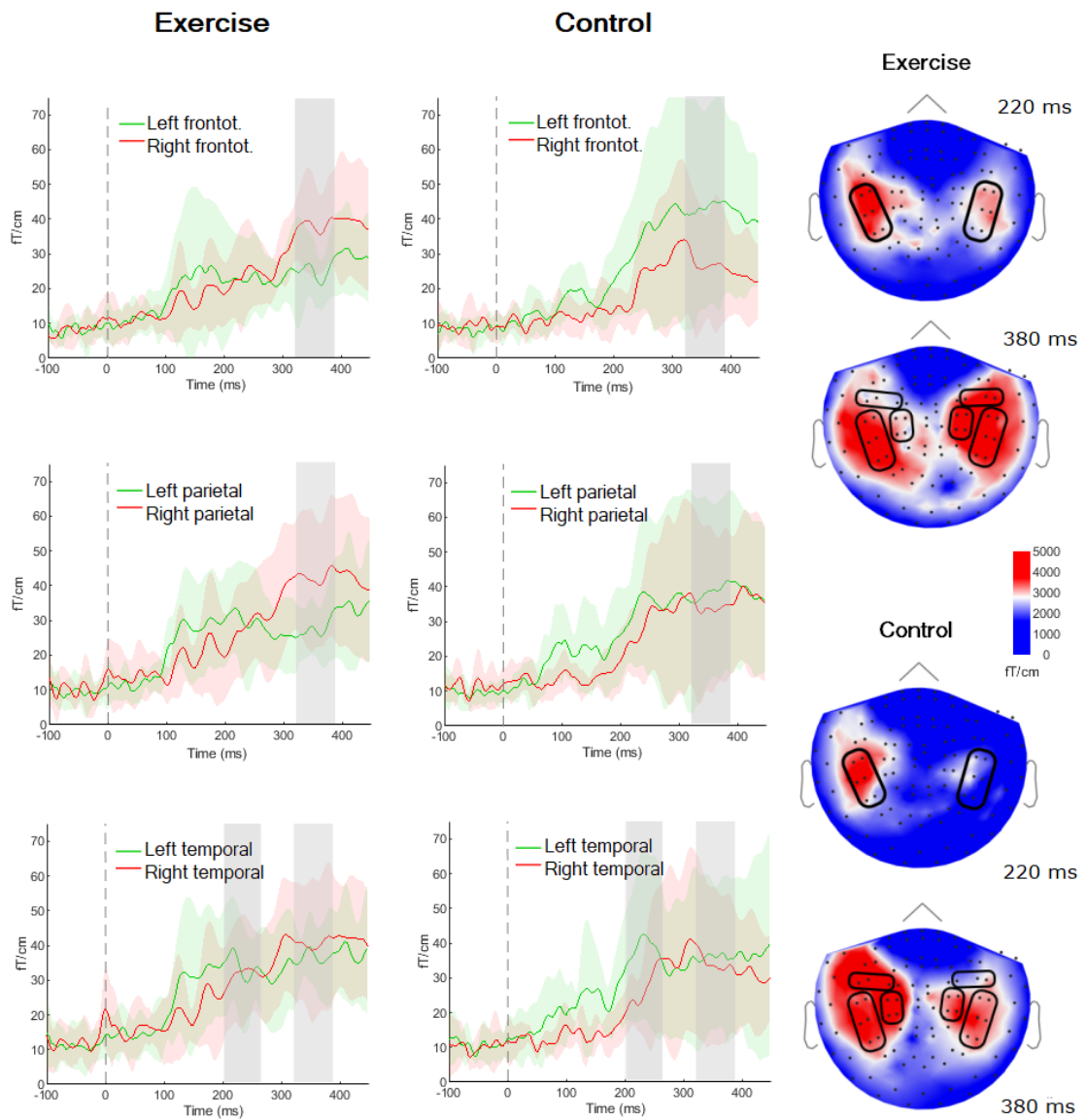
FIGURE 8   Grand average waveforms (±SD) in frontotemporal, parietal, and temporal sensor groups for exercise and control groups, both hemispheres are shown in each graph. The grey-shaded area demonstrates the analyzed time window in each sensor group. Topographic maps show grand averages of both groups in planar gradiometer activity at 220 and 380 ms after stimulus onset. The sensor groups selected for analysis are indicated by black frames.

5.3 Sensory gating and change detection in somatosensory system decline in aging women in *Study III*

Study III examined the effect of aging on attended and non-attended somatosensory brain responses. Results of cognitive tests showed that young adults performed better than older adults on cognitive abilities including memory (RAVLT, ROCF-test, logical memory delayed, digit-span backwards, LNS), processing speed (TMT-A), and executive function (TMT-B, Stroop 1, verbal fluency; p<.05). Young adults also had higher tapping speed and handgrip strength than older adults. Middle-aged adults did not differ from young adults in their cognitive abilities. However, they performed better than older adults on some measures of memory, processing speed and executive function (ROCF-test, TMT-A and -B, Stroop 1, LNS, and tapping speed; p<.05). There were no between-group differences in target detection (84.0 ± 9.4 for young adults, 85.5 ± 12.9 for middle-aged adults, and 84.7 ± 14.7 for older adults) or reaction times (0.440 ± 0.052 s for young adults, 0.454 ± 0.058 s for middle-aged adults, and 0.504 ± 0.112 s) in the *active* oddball condition.

5.3.1 Early responses show declined sensory gating

For early components, larger *passive* deviant and standard M100 components were found in older adults than compared to young adults (p = .005 and p = .044, respectively), in the 82–116 ms and 92–120 ms time windows, respectively (Figure 9). In the *active* condition, a larger standard M100 component was observed for older adults than young adults (p=.008) in the 100 ms–120 ms time window (Figure 10). No differences were found between the middle-aged and young adults. In pairwise analysis within older and young adult groups, deviant M100 also showed a difference between *active* and *passive* conditions for older adults. The *active* condition showed a larger amplitude towards positive polarity and the *passive* condition showed an amplitude towards negative polarity in magnetometers (Figure 11).
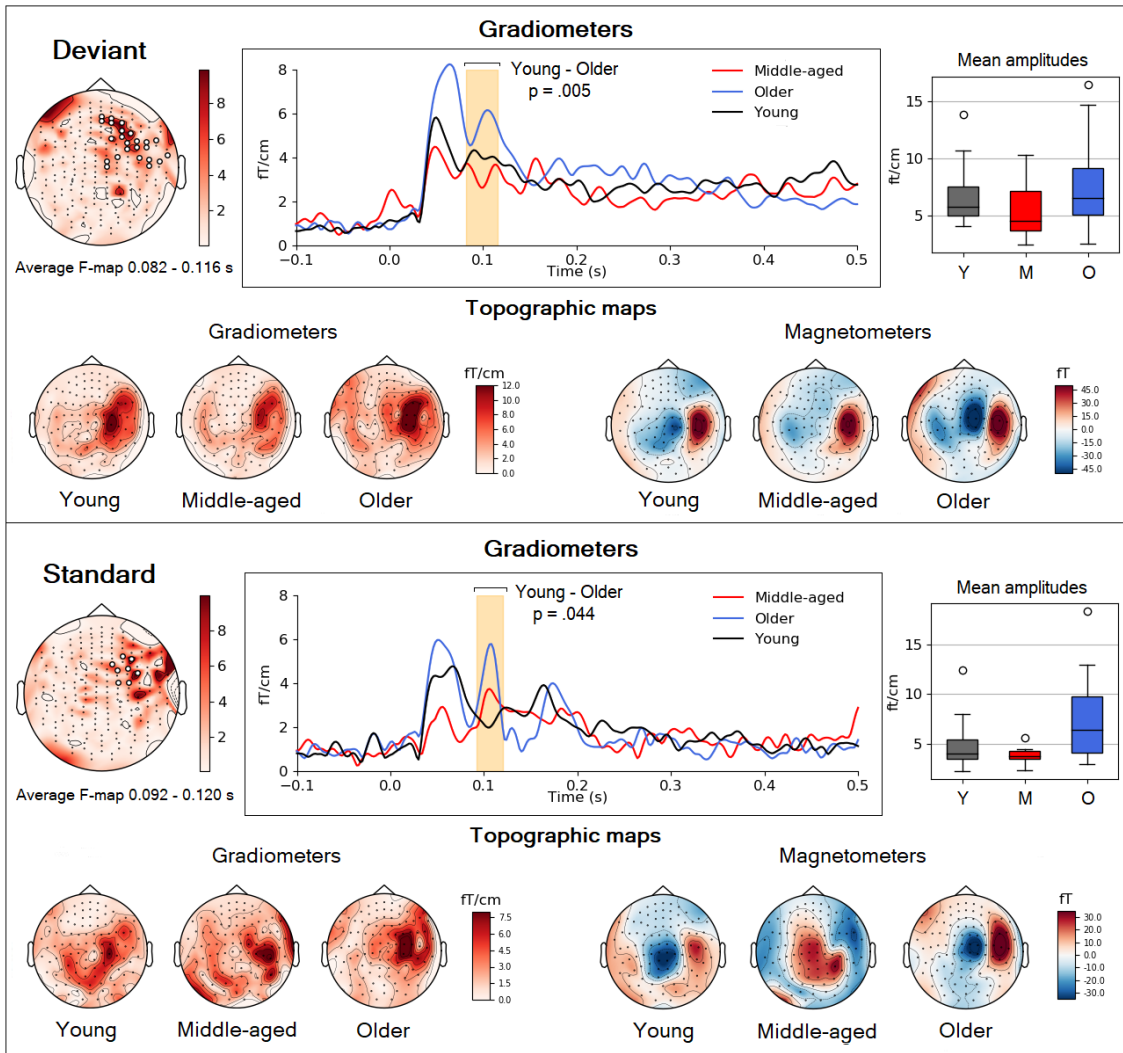
FIGURE 9   Significant clusters for deviant (top) and standard (bottom) M100 compo-
nents between young and older adults revealed by spatiotemporal permuta-
tion test for gradiometers in the passive condition in *Study III*. Sensors show-
ing differences between young and older adults are represented by the high-
lighted dots in the topographic map (top left), with the red color representing
the average F-value distribution. Grand averaged waveforms for young (n =
12), middle-aged (n = 7), and older adults (n = 14) from the sensors of the sig-
nificant clusters (root mean square; RMS) are shown in the center. The yellow
shaded area indicates the significant time windows. Boxplots show the mean
amplitude values of the significant cluster (right, Y = young, M = middle-
aged, O = older) with the median indicated by the horizontal line. Topo-
graphic maps of each group's M100 peak for gradiometers (RMS; left) and
magnetometers (right) are shown at the bottom.

FIGURE 10   Significant cluster for standard M100 component between young and older adults revealed by spatiotemporal permutation test for gradiometers in the active condition in *Study III*. Sensors showing differences between young and older adults are represented by the highlighted dots in the topographic map (top left), with the red color representing the average F-value distribution. Grand averaged waveforms for young (n = 12), middle-aged (n = 6), and older adults (n = 12) from the sensors of the significant cluster (root mean square; RMS) are shown in the center. The yellow shaded area indicates the significant time window. Boxplots show the mean amplitude values of the significant cluster (right, Y = young, M = middle-aged, O = older) with the median indicated by the horizontal line. Topographic maps of each group's M100 peak for gradiometers (RMS; left) and magnetometers (right) are shown at the bottom.

FIGURE 11   Significant cluster for deviant M100 component between passive and active condition for older adults revealed by spatiotemporal permutation test for magnetometers in *Study III*. Sensors showing differences between conditions are represented by the highlighted dots in the topographic map (top left), with the red color representing the average T-value distribution. Grand averaged waveforms for older (solid line, n = 12) and young adults (dashed line, n = 12) from the sensors of the significant cluster (root mean square; RMS) are shown in the center. The yellow shaded area indicates the significant time window. Boxplots show the mean amplitude values of the significant cluster (top right) with the median indicated by the horizontal line. Topographic maps of each group's M100 peak for gradiometers (RMS; left) and magnetometers (right) are shown at the bottom.

5.3.2   Late responses to attended and non-attended change are altered

For later responses, a larger M250 cluster in the gradiometer data was found in the contralateral parietal cortex in young than in older adults in the *passive* condition in the 238–286 ms time window (p=.046; Figure 12). In the *active* condition, there was one cluster with a difference in frontal M350 activity between young and older adults in the gradiometer data in the 255–354 ms time window (p=.044) and two clusters in the magnetometer data in the 252–380 ms (p=.021) and 286–378 ms (p=.025) time windows. The orientation of the magnetometer waveforms and topographic maps indicated more frontal and early activity in older adults than young adults and larger parietal and occipital activity in young than in older adults (Figure 13).
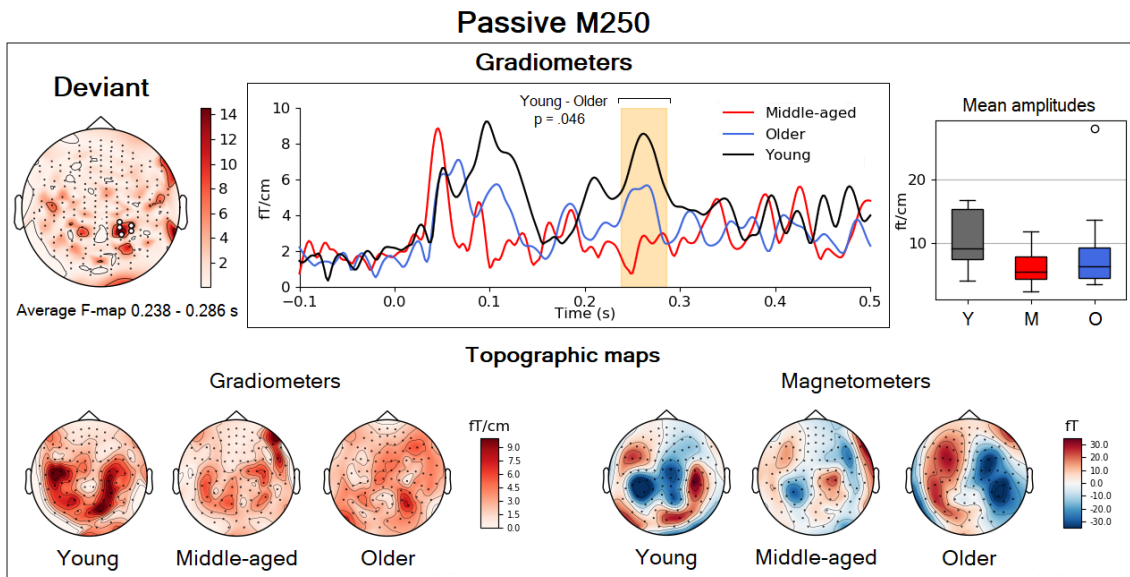
FIGURE 12   Significant cluster for deviant M250 component between young and older adults revealed by spatiotemporal permutation test for gradiometers in the passive condition in *Study III*. Sensors showing differences between young and older adults are represented by the highlighted dots in the topographic map (top left), with the red color representing the average F-value distribution. Grand averaged waveforms for young (n = 12), middle-aged (n = 7), and older adults (n = 14) from the sensors of the significant cluster (root mean square; RMS) are shown in the center. The yellow shaded area indicates the significant time window. Boxplots show the mean amplitude values of the significant cluster (right, Y = young, M = middle-aged, O = older) with the median indicated by the horizontal line. Topographic maps of each group's M250 peak for gradiometers (RMS; left) and magnetometers (right) are shown at the bottom.
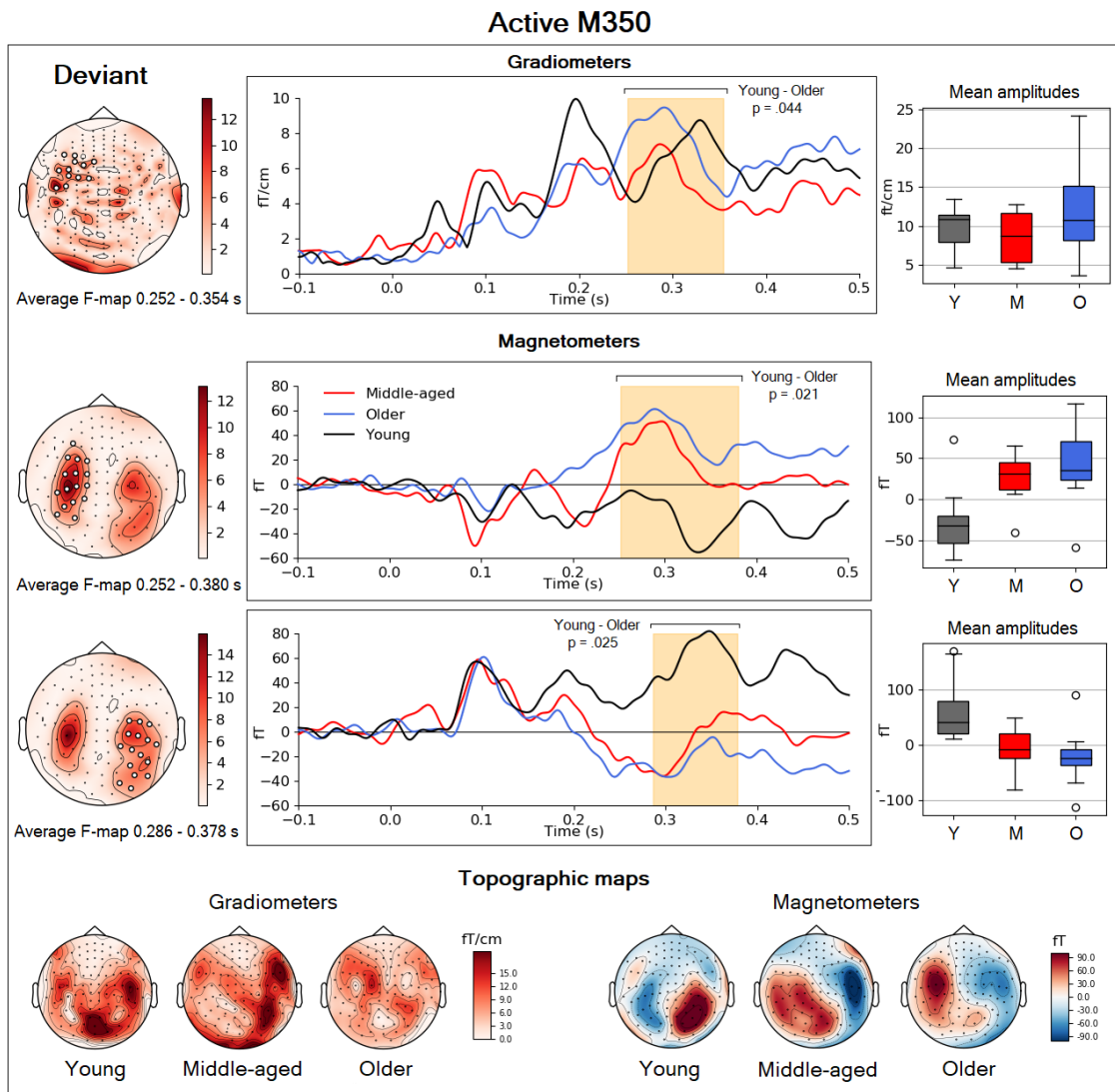
FIGURE 13   Significant clusters for deviant M350 components between young and older adults revealed by spatiotemporal permutation test for gradiometers (top) and magnetometers (bottom) in the active condition in *Study III*. Sensors showing differences between young and older adults are represented by the highlighted dots in the topographic map (top left), with the red color representing the average F-value distribution. Grand averaged waveforms for young (n = 12), middle-aged (n = 6), and older adults (n = 12) from the sensors of the significant clusters (root mean square; RMS) are shown in the center. The yellow shaded areas indicate the significant time windows. Boxplots show the mean amplitude values of the significant clusters (right, Y = young, M = middle-aged, O = older) with the median indicated by the horizontal line. Topographic maps of each group's M350 peak for gradiometers (RMS; left) and magnetometers (right) are shown at the bottom.
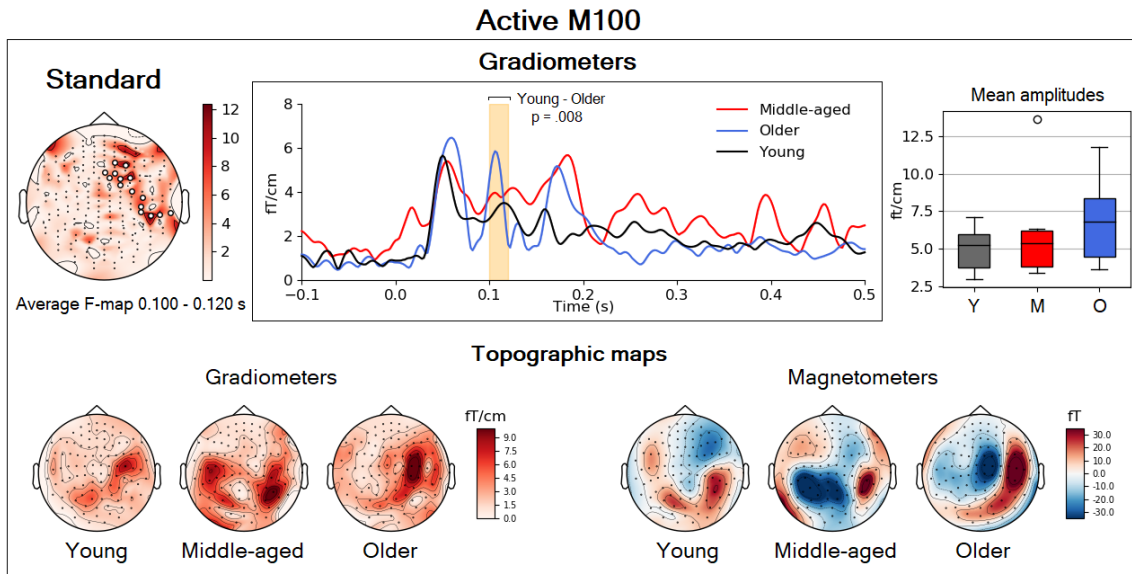
6   DISCUSSION

The present dissertation investigated the influence of aging, and hormonal aging, on somatosensory brain function and peripheral neural mechanisms. *Study I* examined the effect of menopausal transition on TMS-induced inhibitory mechanisms and muscle twitch force potentiation. The SP duration was shorter and MEP amplitude was reduced in late perimenopausal women compared to early perimenopausal women. Furthermore, twitch force potentiation was associated with FSH levels, although no statistical group differences were found. *Study II* investigated somatosensory target detection mechanisms in older men with and without a background of long-term strength training, using the MEG method. Results showed that bilateral brain activity in the somatosensory P3b-related brain component, P3m, was altered in strength-trained older men compared to non-trained controls. *Study III* investigated the somatosensory brain components related to sensory inhibition, change detection, and attention mechanisms in young, middle-aged, and older women. Sensory gating was shown to be reduced in older adults compared to young adults, as evidenced by larger early somatosensory components for task-irrelevant stimuli. Older adults also exhibited altered change detection mechanisms, demonstrated as reduced non-attended P3a-related brain component M250, and altered cortical activity in attended P3b-related brain component M350. The significance of the results of these studies is explored in the following pages.

6.1   Menopausal transition and altered inhibitory and excitatory mechanisms

Perimenopause is the transitional period in a woman's life before final menopause, characterized by fluctuating hormone levels, irregular menstrual cycles, and a variety of symptoms, and can last for several years. As menopause is associated with a decline in muscle contractile quality and function (Bondarev et al., 2018; Sipilä et al., 2013), possible early signs of a decline in neuromuscular

64

properties should be investigated already in the perimenopausal stage. In *Study I*, excitatory and inhibitory mechanisms were investigated using TMS and peripheral electrical stimulation techniques, specifically in TMS-induced excitatory and inhibitory mechanisms and twitch force potentiation, respectively. It was shown that there may be a modulation of these mechanisms already in perimenopause, as indicated by shorter SP duration in moderate force production condition (40 % MVC) and smaller MEP amplitudes in low force production condition (20 % MVC) in late perimenopausal women than in early perimenopausal women. In addition, an association was found between twitch force potentiation and FSH levels.

The findings in *Study* I indicate an alteration in corticospinal inhibitory mechanisms during the menopausal transition period. Modulation of SP duration has been suggested to represent cortical mechanisms (Inghilleri et al., 1993). The menopausal transition is characterized by dramatic changes in hormonal balance (Harlow et al., 2012; Santoro et al., 2021; Talaulikar, 2022). Progesterone has been shown to facilitate GABAergic inhibition and estrogen to suppress it. Studies conducted during different stages of the menstrual cycle have so far mainly indicated a progesterone effect on $GABA_A$ receptor-mediated inhibitory mechanisms (interhemispheric inhibition) and an opposite effect of estrogen (Hausmann et al., 2006; Inghilleri et al., 2004; M. J. Smith et al., 1999, 2002). However, mixed results also exist (Hattemer et al., 2007; Hausmann et al., 2006). In *Study I*, late perimenopausal women had lower E2 and higher FSH levels than early perimenopausal women. Progesterone levels were not measured, but progesterone has been shown to decrease during perimenopause (Santoro et al., 2008). However, it should be recognized that the hormonal balance in the menopausal transition is likely to differ from the fluctuations occurring during the menstrual cycle in women in their reproductive phase when progesterone and estrogen fluctuate systematically. In perimenopause, estrogen levels decrease, but are shown to fluctuate to even higher levels until the final menopausal stage, and progesterone may show long periods of low concentrations along with anovulation (Joffe et al., 2019; Santoro et al., 2008). The results of *Study I* provide preliminary evidence that these shifts in hormonal balance during the menopausal transition may affect the duration of SP, which is mostly mediated by $GABA_B$ receptors. However, there is pharmacological evidence that at the lower range of stimulus intensities SP may reflect the activation of $GABA_A$ receptors (Kimiskidis et al., 2006; Paulus et al., 2008; Rossini et al., 2015). Because the stimulus intensities used were the individually determined lower limb RMTs for each participant in *Study I*, and the measured SP durations were rather short, our stimulus intensities may represent the lower range. Therefore, it cannot be excluded that the differences found in *Study I* are, at least in part, due to $GABA_A$ receptor-mediated inhibitory mechanisms.

In *Study I*, MEP amplitude was also greater in early perimenopausal women than in late perimenopausal women in the 20% MVC condition. Because late perimenopausal women had lower estrogen levels, this finding may represent reduced cortical excitatory mechanisms due to lower estrogen concentrations.

Evidence for the effect of estrogen on motor cortical excitability have previously been presented in women during different stages of menstrual cycle, for example, by Inghilleri et al. (2004), who found reduced facilitation of MEP amplitude in the early follicular phase with low estrogen levels in a repetitive TMS study, and Badawy et al. (2013), who found higher ICF in women during the follicular phase with high estrogen levels compared to luteal phase. However, contradictory results also exist (Hattemer et al., 2007). In *Study I*, the late perimenopausal women had lower E2 levels than the early perimenopausal women. However, considering the hormonal fluctuations, especially in estrogen levels during perimenopause, and the fact that we do not know the specific hormone levels of our participants during the measurements, we cannot draw any further conclusions on the specific hormonal associations on excitatory and inhibitory mechanisms in *Study I*. Furthermore, the differences in SP and MEP characteristics were not present in all force conditions. Therefore, the results should be regarded as preliminary evidence of subtle modulation in excitatory and inhibitory mechanisms.

In *Study I*, twitch force potentiation was negatively associated with FSH levels, suggesting a modulation toward decreasing twitch force potentiation during the menopausal transition. Involuntary muscle contractile properties have previously been associated with hormonal deterioration in menopause, as a study by Finni et al. (2011) found reduced twitch torque in early postmenopausal women without hormone replacement therapy (HRT) background compared to their monozygotic co-twins who had used HRT, while no differences in voluntary force generation were found. Furthermore, estradiol has been shown to modulate force potentiation mechanisms in mice (Lai et al., 2016). In *Study I*, twitch force potentiation was not associated with measured E2 levels. Because of the fluctuating hormone levels in perimenopause, FSH may be a more sensitive marker of perimenopausal progression. In addition, the very subtle fluctuations in E2 may not be detected by the IMMULITE 2000 XPi (Siemens Healthcare Diagnostics, UK), used in *Study I*. Twitch force potentiation has been shown to decrease with age and has been suggested to partially underlie the morphological and functional changes observed in aged muscle (Miller, Herda, Trevino, Sterczala, & Ciccone, 2017). *Study I* provides preliminary evidence that twitch force potentiation may begin to deteriorate along with changes in hormonal balance in perimenopausal women.

The perimenopausal groups showed a difference in plantar flexion strength, but there were no differences between groups in other lower limb strength and performance measures. However, the difference may be indicative of early modulation of muscle function. A study by Bondarev et al. (2018) reported previously lower vertical jumping height in perimenopausal women compared to premenopausal women. Given the importance of plantar flexors for jump execution, the observed difference in plantar flexor strength in *Study I* may indicate a similar decline in lower limb function, despite the absence of significant differences in jumping height between the groups. The findings of *Study I* suggest that other lower limb strength assessments may not yet be

sufficiently sensitive to accurately reflect the physiological changes associated with the current perimenopausal stages.

6.2 Somatosensory P3 modulated in older men with a ten-year strength training background

Age-related cognitive decline is strongly related to changes in the ERP component P3. The association of strength training and the P3b component, which is associated with cognitive processes involved in updating working memory and allocating attentional resources (for a review, see Polich & Kok, 1995), has been scarcely studied. *Study II* aimed to determine, whether the P3m component, recorded with MEG, differs in older men with different training backgrounds. Specifically, the exercise group in *Study II* had a unique consistent background of ten years of weekly strength training, and the otherwise very similar control group had not done any strength training at all. They were similar in their daily PA habits outside the intervention program. The results of *Study II* indicated a modulation of cortical activity between hemispheres in the exercise group compared to the control group. The group*hemisphere effect indicated that the exercise group had stronger activity in the right frontotemporal and parietal regions compared to the left, and the control group had stronger activity in the left similar regions compared to the right. In addition, the control group had a shorter latency in the right temporal sensor group than the exercise group. However, contrary to the hypothesis, no differences in P3m peak or average amplitudes were found between the groups.

The present findings are somewhat inconsistent with the previous findings regarding the effect of strength training on P3b amplitude (Özkaya et al., 2005; Tsai et al., 2015). Özkaya et al. (2005) found an increase in peak-to-peak N2-P3 amplitudes in frontal electrodes after nine weeks of strength training. Tsai et al. (2015) reported diminished P3 amplitudes in their control participants, whereas the training group had similar amplitudes after 12 weeks of strength training. The differences in methodology and sample size may partially explain the variability of results in previous research. For example, in the study by Özkaya et al. (2005), the intervention period was short, only nine weeks, and the results may partly mirror the short-term effects of new activity in many aspects – physical, social, and psychological. They also measured peak-to-peak amplitudes, which may include processes involved in the N2 component. In the study by Tsai et al. (2015), although a decreased P3b amplitude was observed in the non-training group and not in the training group, there were no significant between-group differences after the 12 weeks of intervention. In *Study II*, the initial project did not include MEG data on the participants, which precludes the possibility of analyzing the individual development of P3m brain activity. Therefore, it is not possible to conclude whether the individual development of P3b amplitude differs between the two study groups. Furthermore, the sample size was

relatively small, potentially limiting the ability to detect significant differences in amplitudes. This view is supported by the observation that the measured P3m amplitudes showed considerable interindividual variability.

In *Study II*, P3m was detected as bilateral activity in both groups that parallelled somatosensory P3b activity and sources detected in previous studies (Naeije et al., 2018; Tarkka et al., 1996; Valeriani et al., 2001). Because topographic maps indicated a difference in the distribution of P3m between groups, a mixed model analysis was performed, which included both hemisphere and group effects. The detected effects, along with the amplitudes and confidence intervals, indicated that the exercise group exhibited stronger P3m activity in the right than left parietal and frontotemporal sensor groups while the control group demonstrated stronger P3m activity in the left than right frontotemporal sensor group. In somatosensory P3b studies, this type of lateralization has not been reported in prior source analyses to our knowledge (Tarkka et al., 1996; Valeriani et al., 2001), although, Valeriani et al. (2001) reported an additional unilateral frontal source for P3b, contralateral to stimulation with young adults. Interestingly, a pronounced P3b amplitude in the right hemisphere has been reported previously in auditory P3b studies (Frodl et al., 2000; Gilmore et al., 2009), which has been theorized to arise from a right hemispheric network that is associated with working memory, sustained attention, and target detection. Furthermore, McDowell et al. (2003) have reported differences in P3b laterality in young and older adults, which was associated differently with PA backgrounds. The MEG technique employed in *Study II* may be more sensitive to lateralization than previous EEG recordings. It can be hypothesized that the exercise group in *Study II* was able to use the right hemispheric network more effectively in the stimulus detection task. However, further conclusions would require further investigation.

Regarding the P3b component, a distinctive observation that occurs with aging is the frontal topographic distribution compared to the typical parietal distribution reported in young adults (van Dinteren et al., 2014a). In the topographic maps of *Study II*, a bilateral frontal distribution is observed in both exercise and control groups. Another explanation for the observed hemispheric differences may be that they result from a difference in additional frontal brain areas used for cognitive task performance. While the functional significance of the age-related frontal shift of P3 is not fully understood, it is theorized to result from compensatory mechanisms to enhance the cognitive function of the aging brain or additional neural networks used for task performance. Our participants performed similarly in terms of target detection and reaction times, so we cannot draw further conclusions on whether the difference in hemispheric activity is related to processing speed or accuracy. In addition, we do not have further cognitive function measures for the participants and cannot discuss whether the asymmetry is related to specific aspects of cognitive function. Both of our groups of aged individuals may use compensatory brain mechanisms for the deviant detection task, but perhaps there are differences in how this occurs. Overall, the

effects of strength training, exercise, and aging on somatosensory P3m activity require further research and larger sample sizes.

In the P3m latency analysis with sensor groups, the control group exhibited a shorter latency in the right temporal region than the exercise group. P3b latencies have been demonstrated to increase with age in late adulthood and to correlate with poorer cognitive performance (Pelosi et al., 1992; van Dinteren et al., 2014b). In contrast to the findings in *Study II*, previous studies have demonstrated that PA has resulted in a shorter P3b latency in young individuals. However, the results in the aging population, are highly variable (for a review, see Kao et al., 2019). No studies have found an association between strength training and P3b latency in aging individuals. Shorter latency may indicate faster processing of the target stimulus in the control group. However, in the sensor group P3m values in *Study II*, the peak of the waveform may not properly describe the true latency of the P3b because multiple sensors and processes affect the peak amplitude of the wave. Therefore, the observed peak latency may not be a reliable indicator of the processing speed associated with target detection. Furthermore, the observed difference in P3m latency was not identified in other regions with more pronounced P3m amplitude. Consequently, it is not possible to draw any further conclusions regarding this finding.

6.3 Somatosensory gating and change detection mechanisms are modulated in older adults

It has been proposed that sensory gating and change detection are affected by aging (Alain et al., 2022; Anderer et al., 1996; Ruohonen et al., 2020; Spooner et al., 2020; Stothart & Kazanina, 2016; Strömmer et al., 2014, 2017; Terrasa et al., 2018). The results of *Study III* indicated a decline in somatosensory gating of task-irrelevant stimuli and change detection mechanisms of both non-attended and attended deviant stimuli in older adults compared to young adults, as utilizing the oddball paradigm. Specifically, a larger M100 amplitude was observed in older adults than young adults for standard stimuli in both active and passive stimulation conditions, and deviant stimuli only in the passive condition. Regarding the late components, older adults showed reduced M250 amplitude compared to young adults in the passive condition. Furthermore, the M350 showed an alteration towards a more frontal topographic distribution in older adults compared to young adults in the active condition. Middle-aged adults did not reveal significant differences from young adults.

In *Study III*, older adults presented larger M100 amplitudes than young adults, which might indicate poorer sensory inhibition (i.e. sensory gating). Notably, this alteration was only present for the task-irrelevant stimuli (i.e. standard stimuli in both active and passive conditions and deviant stimuli in the passive condition) but not for task-relevant, target stimuli (i.e. deviant stimuli in the active condition). This result is in line with previous studies that have

demonstrated larger early components in older than young adults in auditory oddball paradigms (Alain & Woods, 1999; Amenedo & Díaz, 1998a; Anderer et al., 1996; Ruohonen et al., 2020; Stothart & Kazanina, 2016). Alain et al. (2022) also demonstrated larger early evoked potentials in auditory, visual, and somatosensory domains in older adults compared to young adults, which were all correlated. In an EEG study by Strömmer et al. (2017), the P50 and N80 elicited in a passive somatosensory oddball design were larger for older than younger adults for both standard and deviant stimuli. However, the group difference was no longer significant when the analysis was controlled for stimulus intensities, which were higher for the older than younger adults, a common finding in electrical thresholds (Kemp et al., 2014). On the other hand, Bolton & Staines (2012) reported a difference in the amplitudes of the unattended standard P100, such that older adults showed a more positive P100 than young adults. P100 amplitudes were similar between the two groups when the standard was attended. This finding and the results of *Study III* may suggest that inhibition of task-irrelevant, unattended somatosensory stimuli is impaired in older adults, while processing of somatosensory stimuli in the SI is preserved when attention is present. Another possible explanation is that older adults recruit more or engage different neural resources to enhance sensory processing efficiency when attention is not present. The deviant M100 may also partly reflect enhanced neural mechanisms for change detection. The discrepancy in findings between task-irrelevant and task-relevant stimuli suggests that attention direction influences amplitude enhancement, which provides support for the hypothesis that adaptation to stimuli outside of attention is reduced in older adults.

It has been suggested that the loss of sensory inhibitory function in aging is due, at least in part, to a decline in PFC function (for a review, see Hedden & Gabrieli, 2004; Yamaguchi & Knight, 1990). The PFC has been shown to play a role in the suppression of irrelevant information during the early stages of sensory processing, as evidenced by studies involving individuals with prefrontal lesions and by studies of continuous theta burst stimulation of the dorsolateral PFC (Bolton & Staines, 2011, 2014). Furthermore, studies have demonstrated that aging is associated with volume loss, particularly in the PFC (for a review, see Kaup et al., 2011; Raz et al., 1998; Resnick et al., 2003). In a recent study by Alain et al. (2022), it was demonstrated that there are age-related differences in phase synchrony between prefrontal regions and sensory cortices. This finding suggests that age-related changes in prefrontal functioning may be a potential underlying cause of deficits in sensory inhibition. No specific analysis of PFC activity was performed in *Study III*, and therefore no further conclusions can be drawn about the origin of the differences found in the present M100 components.

Studies in the auditory domain have suggested that the amplitudes of early brain potentials for repetitive stimuli with latencies of around 100 ms increase already in middle age (Amenedo & Díaz, 1998b; Anderer et al., 1996). To my current knowledge, only Reuter et al. (2013) have investigated early brain components for standard somatosensory stimuli in middle-aged individuals. No

differences were identified between the young and middle-aged groups, although the topographic maps suggested that modulation might already be present between the groups. The absence of findings may be attributed to the fact that the participants concentrated their attention on the standard stimuli presented in the experiment. In *Study III*, no significant differences were observed in the early components between young and middle-aged adults. However, the sample size for the middle-aged group was limited and might not have enough power to reveal significant differences. Further research is needed regarding the inhibition of somatosensory stimuli in middle-aged adults.

In *Study III*, older adults also showed a reduced M250 component in the contralateral parietal area compared to young adults. The M250 component most likely corresponds to the P3a component widely reported in EEG studies (for a review, see Polich & Criado, 2006), which has been found in very similar latency ranges of 200–300 ms in the somatosensory modality (Kangas et al., 2022; Shen et al., 2018; Strömmer et al., 2017). This finding suggests an alteration in somatosensory attention-shifting mechanisms in aging. Previously, studies in the auditory, visual, and somatosensory modalities have suggested a linear decrease in P3a amplitude with age (Fjell & Walhovd, 2003, 2004; Yamaguchi & Knight, 1991). A somatosensory ERP study found no amplitude difference between young and older adults in the somatosensory P3a with a passive oddball paradigm (Strömmer et al., 2017). This discrepancy may be related to the different methodologies used in these studies, as the recording in *Study III* was based on a MEG method. However, a previous EEG study by Strömmer et al. (2014) reported a difference in late MMR at a latency range of 250–290 ms, similar to M250 in *Study III*. This may indicate that the component included P3a-related processes. P3a, elicited in a passive oddball condition, is considered to reflect stimulus evaluation processes and an automatic reorientation of attention to the deviant stimulus (for reviews, see Friedman et al., 2001; Polich & Criado, 2006). The major neural networks generating P3a across different sensory modalities have been suggested to be located in the frontal lobe, hippocampus, and anterior cingulate cortex (Knight, 1996; Wronka et al., 2012; for review, see Friedman et al., 2001). The topographic maps in *Study III* suggested bilateral centro-parietal activity in this latency window, particularly in young adults, whereas activity was shifted more to frontal areas in older adults.

Surprisingly, no significant difference was found within the sMMR latency range between the groups in *Study III*. Previous ERP studies have found differences between younger and older adults for the sMMR (Strömmer et al., 2014, 2017). It is important to note, however, that in the previous study conducted by Strömmer et al. (2014), the MMR latency range was quite late. Nevertheless, previous reviews on auditory mismatch negativity (MMN) indicate a reduction in amplitude in older adults relative to young adults (Cheng et al., 2013; Ruzzoli et al., 2012), suggesting an impairment in the change detection of sensory information in older adults. Furthermore, the N-methyl-D-aspartate (NMDA) receptor density has been shown to decrease with age (Müller et al., 1994), which has been shown to contribute to MMR generation in pharmacological studies

(Kreitschmann-Andermahr et al., 2001). It has also been proposed that the decline in inhibition of repetitive sensory information affects the higher-order predictive coding of rare, deviant stimuli – a phenomenon also observed as larger M100 components in the present dissertation. The reason for the lack of group differences in MMR in *Study III* is unknown, but it may be that the whole-head model was not sufficient to detect the differences or that the sample size was too small. It should also be noted that the standard and deviant stimuli were analyzed separately rather than the difference waves, a more common method in MMN research.

In the active condition of *Study III*, the results also revealed differences in the M350 component, corresponding to P3b, between young and older adults. This difference was found in sensor-space analyses with both gradiometers and magnetometers. Significant clusters from spatiotemporal permutation tests and topographic activity indicated that the M350 component was located parietally and occipitally in young adults compared to older adults, whose M350 component activity was more frontal. This finding is consistent with previous evidence of a frontal shift in P3b during aging (Alperin et al., 2014; Reuter et al., 2017; van Dinteren et al., 2018). Although the frontal shift of P3b is a common finding in the P3b literature, the functional significance of this phenomenon remains unclear (Alperin et al., 2014; Kamp, 2020; van Dinteren et al., 2014a). It has been suggested that it results from compensatory processes, in which frontal brain areas are proposed to be used for better cognitive function (for review, see Cabeza et al., 2018; Kang et al., 2022; van Dinteren et al., 2014a). However, this theory has been challenged as the frontal distribution of P3b has been associated with longer response times (Reuter et al., 2017), and target detection has been associated with parietal amplitudes but not frontal amplitudes (Kamp, 2020). It has therefore been suggested that the frontal shift of P3 is associated with less efficient and slower processing and that older adults simply recruit additional cognitive control for task performance. The amplitudes of frontal and parietal P3b have been shown to develop separately across the lifespan, with parietal P3b amplitude increasing from childhood until about age 20 and then gradually decreasing with age, whereas frontal P3b amplitude increases until middle age, and then decreasing minimally (van Dinteren et al., 2014a). Recently, principal component analyses have suggested that the P3a component, representing attentional shifting and stimulus evaluation mechanisms, contributes to P3b activity (Alperin et al., 2014; Kamp, 2020). However, this interpretation requires further investigation.

Interestingly, middle-aged adults showed a similar pattern of activity in the M350 waveforms and topographies as older adults in *Study III*. However, no differences were found between young and middle-aged adults in the M350. Parietal P3b has been shown to decrease linearly with age (van Dinteren et al., 2014a). In the somatosensory domain, Reuter et al. (2013) reported similar amplitudes between frontal electrodes and central and parietal electrodes in late middle-aged adults, whereas young and early middle-aged adults showed lower amplitudes in frontal electrodes compared to central and parietal electrodes in a

tactile stimulation paradigm. However, they did not yet show amplitude differences between the groups, which might be due to their small study sample (N=8 in the late middle-aged group). It may be that the study sample in *Study III* was similarly too small to detect differences between groups, as the middle-aged group in *Study III* consisted of only 6 participants in the active condition. Furthermore, we did not analyze differences between the frontal and parietal brain regions within the groups. The observed topographic activity may indicate an age-related shift to frontal P3b already in middle-aged adults, but this was not yet statistically different from young adults.

The older adults in *Study III* performed more poorly on cognitive tests requiring a variety of cognitive abilities, including inhibition, memory, and processing speed when compared to young adults. Middle-aged adults did not yet exhibit differences in cognitive abilities compared to young adults.

6.4 Methodological considerations and limitations

There are limitations to the current thesis that should be considered. The major limitation of *Study I* was the lack of navigated TMS and individual brain images, which would allow more precise localization of the optimal stimulation site. The leg motor areas are relatively small, located deep in the interhemispheric fissure, and the optimal stimulation locations are less segregated than those of the hand muscles (Niskanen et al., 2010). Consequently, identifying the optimal stimulation location may be challenging, and higher intensities may be necessary to elicit measurable MEPs when compared to the hand (Kesar et al., 2018). For this reason, we used a stimulus intensity that was the visually detected lower limb RMT for each participant. This may pose a challenge to the reliability and generalizability of the findings, as different stimulus intensities have led to disparate results in previous research. For example, changes in SP after fatiguing exercise have been found at lower TMS intensities but not at higher intensities (Temesi et al., 2014). Because of these challenges, we controlled our analyses for stimulator output intensities used for each participant.

It should be noted that the MEP amplitudes in *Study I* were not based on the M-wave ratio. Therefore, the results for MEP amplitude findings should be interpreted with caution. Furthermore, the MEP-SP ratio, proposed by Hupfeld et al. (2020) as a means of differentiating between inhibition and mechanisms affecting both MEP amplitude and SP duration, was not measured. Therefore, analogous mechanisms may be responsible for the observed differences in MEP amplitudes and SP durations. Furthermore, the number of TMS trials to achieve each MEP and SP average was rather small (Rossini et al., 2015; Škarabot et al., 2019). Furthermore, the IMMULITE 2000 XPi (Siemens Healthcare Diagnostics, UK) method of measuring extremely low E2 levels is not without some degree of inaccuracy, which may result in the most subtle variations going undetected. It is therefore possible that not all associations may have become apparent. However, the results for E2 levels were found to be consistent with both FSH

levels and menstrual histories. The sample size for *Study I* was relatively small, but the study was distinctive due to the accurate identification of menopausal status using menstrual cycle and FSH concentrations, along with the fact that the groups were comparable in age and other relevant characteristics.

A major limitation of *Studies II* and *III* is the small sample size. In *Study II*, the small sample size was due to the various exclusion criteria for MEG measurements and the fact that our participants were part of a larger, ten-year project. Four participants in the control group were new recruits and therefore were not part of the original randomization. They also did not participate in the baseline and follow-up measurements of the original study. Particularly in *Study III*, the sample of middle-aged adults was rather small, which may have affected the results, and possible changes in somatosensory processing may not have been detected. In *Studies II* and *III*, the main analysis was limited to the sensor level, and no individual source analysis was performed. We did not have individual structural magnetic resonance brain images, which is particularly noteworthy for older adults, as current structural templates are based on the brain structure of young adults and may significantly limit the accuracy. The multiple sources and networks may also present a challenge concerning reliable localization, particularly in the case of the latter components. The main research question was to determine the differences in somatosensory brain responses between the age groups and the exercise and control groups. Therefore, a sensor-level analysis was selected as the most appropriate methodology for answering this question.

In *Study III*, the analysis of the M190 component corresponding to MMR was performed separately for standard and deviant stimuli, rather than calculating difference waves, as is commonly done in MMN research. This method was chosen because of the poorer signal-to-noise ratio of difference responses, and the fact that such an analysis cannot define whether the detected group differences are related to the standard or deviant stimuli (Kremláček et al., 2016). In addition, the analysis of all components in *Study III* was based on a spatiotemporal cluster-based permutation test on whole-head activity and therefore, smaller effects may not be detected here.

In *Study II*, the measurements were a late addition to an ongoing project, and thus MEG registration was not performed during the baseline or follow-up measurements. Consequently, no information is available regarding the long-term changes in the P3m activity. Furthermore, the administration of formal cognitive tests to obtain detailed information on the participants' cognitive abilities was not feasible. However, the participants in all three studies were free of any diagnosed neurological or psychiatric diseases and medications affecting the central nervous system. The participants were of normal weight and exhibited comparable physical activity habits between groups in all three studies.

6.5 Future directions

The results of the present dissertation complement the previous evidence of age-related changes in somatosensory electrophysiological brain responses and give preliminary evidence of the effect of hormonal aging on neuromuscular mechanisms. However, further research is necessary, as there are still discrepancies among studies and methodologies.

Firstly, *Study I* should be replicated with larger sample sizes to confirm preliminary interactions in the perimenopausal stage and TMS-induced inhibitory and excitatory mechanisms. Further research is also needed with premenopausal and postmenopausal women included, to determine whether the modulation is present across all menopausal stages, and if it is still present post menopause. In addition, the effect of hormonal balance and aging on TMS-induced SP requires more investigation, as there is still a discrepancy in previous findings. The complex inhibitory mechanisms observed in SP should be further investigated, especially how cortical mechanisms are involved in the SP duration, to understand the mechanisms involved in the modulation of SP. Furthermore, as the relationship between FSH levels and twitch force potentiation may indicate decreasing twitch potentiation mechanisms, possibly due to changing hormonal levels during the menopausal transition, this interaction should also be investigated in pre and postmenopausal women to understand the possible decline in twitch properties throughout the menopausal transition. These research topics are crucial in understanding the complex effect of menopausal transition and menopause on the nervous system. The relationship of these measures with physical abilities should also be studied to understand the underlying mechanisms of muscle function decline associated with menopause.

The effect of strength training on P3m investigated in *Study II* raises the question of whether the observed differences may be reflected in sources of P3b generation. Source analyses could reveal potential differences in frontal sources in aging individuals with different exercise backgrounds and whether training can modulate the age-related changes in the P3b generation. Understanding the effects of different exercise modalities on age-related brain changes would help promote preventive exercise methods. Similarly in *Study III*, the underlying mechanisms of the detected differences in early and late components should be further investigated. Future investigations of somatosensory early and late brain responses should focus on detailed source localization with individual brain images. The mechanisms behind enhanced early brain components in older adults should be further investigated to understand the balance between inhibitory and excitatory mechanisms in early sensory processing in aging. Furthermore, the use of novel sensor technology may facilitate the localization of deeper brain sources, extending the capabilities of previous investigations, particularly regarding the P3 component, which is a result of a complex network of neural circuits.

Study III also raises the question, of whether changes in somatosensory brain responses could already be observed in middle-aged adults, especially for late responses. Thus, somatosensory P3b should be further studied in middle-aged individuals with larger study samples. Furthermore, the somatosensory MMR and P3a should be investigated with more consistent methods to determine the effect of aging on the complex neural mechanisms associated with automatic somatosensory change detection.

Finally, somatosensory brain components should be studied further in both healthy and diseased aging since they might have the potential for clinical applications in the early detection and prevention of cognitive decline.

6.6 Conclusions

The results of this dissertation indicate that the advanced perimenopausal stage affects the excitatory and inhibitory balance of neuromuscular mechanisms. The findings suggest a subtle modulation toward a decrease in TMS-induced inhibition in late compared to early perimenopausal women and a possible decline in muscle twitch force potentiation during menopausal transition. The results also suggest an age-related modulation in cortical processing of both non-attended and attended somatosensory stimuli. Older adults showed reduced sensory gating of task-irrelevant somatosensory stimuli compared to young adults. Moreover, older adults demonstrated reduced attention shifting and altered working memory updating compared to young adults. Ten-year strength training background in older men did not result in a difference in P3m amplitudes compared to non-strength-trained controls. However, the groups exhibited differences in the hemispheric distribution of the P3m component, which is associated with the allocation of attentional resources. This finding suggests that long-term strength training may modulate the age-related compensatory processes in brain function.

YHTEENVETO (SUMMARY IN FINNISH)

Ihmisen ikääntyessä tapahtuu eteneviä muutoksia niin kognitiivisessa kuin motorisessakin toiminnassa, mikä vaikuttaa laajasti yksilön toimintakykyyn ja elämänlaatuun. Muutokset kognitiossa pohjautuvat ikääntymisen tuomiin aivojen rakenteellisiin ja toiminnallisiin muutoksiin, ja esimerkiksi aivojen kyky käsitellä aisti-informaatiota muuttuu. Ikääntyneen aivojen ajatellaan suodattavan heikommin ympäristön aistitulvaa, jonka myötä aivojen on hankalampaa keskittyä tehtävän kannalta oleellisiin ärsykkeisiin sekä niiden käsittelyyn, kuten muutoksen havaitsemiseen ja tarkkaavaisuuden ylläpitoon. Toisaalta muutoksiin kognitiivisessa toiminnassa voi vaikuttaa sekä ennaltaehkäisevästi että myöhemmin iäkkäänäkin, esimerkiksi fyysisen aktiivisuuden ja liikuntaharjoittelun avulla.

Menopaussin on todettu vauhdittavan useita ikääntymiseenkin liitettyjä kehon muutoksia, kuten lihasten toiminnan ja voiman heikkenemistä. Mekanismit näiden muutosten taustalla eivät kuitenkaan ole täysin selviä. Menopaussin aikana naisen elimistön sukupuolihormonipitoisuudet muuttuvat: estradiolin pitoisuus laskee ja follikkelia stimuloivan hormonin (FSH) pitoisuus kasvaa. Naishormonaalisten muutosten on todettu olevan yhteydessä esimerkiksi neuroinflammaatioon, mitokondrioiden vajaatoimintaan ja synapsien vähentymiseen. Myös useat perimenopausaaliset, eli menopausaalisen siirtymän aikaiset oireet ovat luonteeltaan neurologisia, kuten masennus ja kognition muutokset. Kyky liikkua koordinoidusti arjen toiminnoissa vaatii yhtäaikaista eksitatorista, eli kiihdyttävää, ja inhibitorista, eli ehkäisevää hermostollista kontrollia. Tästä syystä olisi tärkeä selvittää, kuinka menopausaalinen siirtymä vaikuttaa hermoston ja hermolihasjärjestelmän toimintaan.

Tämän väitöskirjan tarkoituksena oli selvittää ikääntymisen vaikutusta somatosensoriseen ja motoriseen aivotoimintaan. Erityisesti tarkoituksena oli selvittää ikääntymisen tuomia muutoksia aivojen somatosensorisessa gating-mekanismissa sekä esitietoisessa että tietoisessa muutoksen havaitsemisessa ja tarkkaavaisuuden suuntaamisessa. Lisäksi selvitettiin, onko pitkäaikaisella ja säännöllisellä voimaharjoittelulla vaikutusta ikääntyneen aivojen tietoiseen muutoksen havaitsemisjärjestelmään. Väitöskirjan toisena tavoitteena oli selvittää menopausaalisen siirtymävaiheen vaikutusta hermoston inhibitoriseen ja eksitatoriseen toimintaan. Tutkimuksessa käytimme moderneja aivokuvantamis ja -stimulaatiomenetelmiä: magnetoenkefalografiaa (MEG) ja transkraniaalista magneettistimulaatiota (TMS).

Väitöskirjan ensimmäisessä osatutkimuksessa tutkittiin perimenopaussin aikaisia muutoksia TMS:n aikaansaamassa inhibitiossa sekä lihaksen sähköisesti aiheutetun voimantuoton potentoitumisessa. Tähän poikkileikkaustutkimukseen osallistui 63 naista, joista 28 oli perimenopaussin alkuvaiheessa ja 35 perimenopaussin myöhäisemmässä vaiheessa, mikä määriteltiin FSH:n sekä kuukautispäiväkirjan perusteella. Tutkittavilta mitattiin TMS:n aikaansaamaa motorista potentiaalia ja sen jälkeistä, niin kutsuttua hiljaista jaksoa etummaisesta säärilihaksesta 20 %, 40 % ja 60 % maksimaalisesta voimatasosta, sekä lihasak-

tivaation jälkeisen sähköisesti aiheutetun lihasnykäyksen voiman potentoitumista nilkan ojennuksessa. Tutkimuksessa perimenopaussin myöhäisemmässä vaiheessa olevilla naisilla havaittiin lyhempi hiljaisen jakson pituus 40 % voimatasolla sekä pienempi motorinen potentiaali 20 % voimatasolla. Lisäksi lihasnykäyksen voimantuoton potentoituminen korreloi negatiivisesti FSH tason kanssa, vaikka ryhmien välistä eroa ei löydetty. Tulokset osoittavat, että menopausaalisen siirtymän aikaisilla naishormonien tason muutoksilla voi olla jo vaikutusta hermolihasjärjestelmän eksitatoriseen ja inhibitoriseen toimintaan.

Toisessa osatutkimuksessa tutkittiin pitkäaikaisen ja säännöllisen lihasvoimaharjoittelun vaikutusta ikääntyneiden miesten P3-aivovasteeseen, joka on yhdistetty tietoiseen tarkkaavaisuuden resurssien kohdentamiseen ja työmuistin päivittämiseen, ja todettu pienentyvän ja muuttuvan ikääntyessä. Tutkimukseen osallistui iältään 74–82-vuotiaita miehiä, joista yhdeksän oli tehnyt säännöllistä lihasvoimaharjoittelua kymmenen vuoden ajan, ja kahdeksan samanikäistä verrokkia ilman lihasvoimaharjoittelutaustaa. Heiltä mitattiin somatosensorista P3 aivovastetta MEG:lla (P3m) hyödyntäen sähköistä stimulaatiota oddball-koeasetelmassa, jossa toistuva ja tästä epäsäännöllisesti poikkeava kohdeärsyke annettiin oikean jalan varpaisiin. Tutkimuksessa havaitsimme ryhmien välillä eroa P3m aivovasteen aikaisessa aktiivisuudessa aivopuoliskojen välillä. Selvää eroa ei kuitenkaan löydetty aivovasteen voimakkuudessa. Tulokset viittaavat muutoksiin työmuistin päivittämiseen liittyvän aivovasteen aktiivisuudessa, mahdollisesti erilaisten ikääntymisen tuovien kompensatoristen mekanismien myötä.

Kolmannessa osatutkimuksessa tarkasteltiin ikääntymisen vaikutusta somatosensorisiin aivovasteisiin niin tarkkaavaisuuden alla kuin tarkkaavaisuuden ulkopuolellakin. Tutkittavat koostuivat 15 nuoresta 20–28-vuotiaasta, seitsemästä keski-ikäisestä 46–56-vuotiaasta ja 15 ikääntyneestä 64–78-vuotiaasta naisesta. Heiltä mitattiin somatosensorisia aivovasteita MEG:lla, sekä aktiivisen että passiivisen oddball-koeasetelman aikana, jossa toistuva ja poikkeava ärsyke annettiin vasemman käden sormiin. Tutkimuksessa havaitsimme ikääntyneillä voimakkaammat 100 ms latenssin aivovasteet nuoriin verrattuna sellaisten ärsykkeiden jälkeen, jotka olivat tarkkaavaisuuden ulkopuolella sekä aktiivisessa että passiivisessa koeasetelmassa. Ikääntyneillä havaittiin myös ero aktiivisen ja passiivisen poikkeavan havainnon aivovasteen välillä. Tulos viittaa ikääntyneiden heikentyneeseen irrelevanttien ärsykkeiden suodattamiseen. Lisäksi ikääntyneillä havaittiin heikentynyt muutoksen havaitsemiseen ja tarkkaavaisuuden automaattiseen suuntaamiseen liittyvä vaste sekä mahdollista frontaalista siirtymää työmuistin päivittämiseen liittyvän aivovasteen aktiivisuudessa. Keski-ikäisten aivoaktiivisuus näytti samansuuntaista muutosta kuin ikääntyneillä, mutta he eivät eronneet tilastollisesti nuorista. Keski-ikäisten pieneksi jäänyt otos saattoi kuitenkin olla syynä tähän.

Tämän väitöskirjan tulokset osoittavat, että ikääntyneen aivojen kyky suodattaa aisti-informaatiota, havaita muutoksia ja päivittää työmuistia on heikentynyt, ja somatosensorinen oddball-koeastelema osoittaa näitä muutoksia luotettavasti. Ikääntyneen aivojen kompensatoriset mekanismit ovat myös nähtävissä somatosensorisen ärsykkeen luokitteluun ja työmuistin päivittämiseen liittyvissä

aivovasteissa tarkkaavaisuuden alla ja pitkään toteutettu lihasvoimaharjoittelu saattaa vaikuttaa tähän kompensaatiomekanismiin. Samansuuntaista aivoaktiivisuuden muutosta pystyttiin havaitsemaan myös keski-ikäisten keskiarvoaivovasteista ilman muutoksia kognitiivisessa toiminnassa, mutta näitä muutoksia emme pystyneet todentamaan tilastollisesti. Lisäksi keski-ikäisillä perimenopausaalisilla naisilla oli nähtävissä mahdollisia ensimmäisiä merkkejä eksitatorisen ja inhibitorisen toiminnan muutoksista lihashermojärjestelmässä. Lisätutkimukset ovat kuitenkin tarpeen tulosten vahvistamiseksi sekä monimuotoisten mekanismien ymmärtämiseksi. Tulosten perusteella on mahdollista, että voimme hyödyntää näitä somatosensorisia ja motorisia muuttujia havaitsemaan muutoksia kognitiivisessa ja motorisessa toiminnassa jo ikääntymisen aikaisessa vaiheessa.

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ORIGINAL ARTICLES

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PERIMENOPAUSAL WOMEN SHOW MODULATION OF EXCITATORY AND INHIBITORY NEUROMUSCULAR MECHANISMS

by

Pesonen, H., Laakkonen, E. K., Hautasaari, P., Aukee, P., Kovanen, V., Sipilä, S., Finni, T. & Tarkka, I. M. 2021

RESEARCH ARTICLE

Perimenopausal women show modulation of excitatory and inhibitory neuromuscular mechanisms

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Abstract

Background: Menopausal transition exposes women to an early decline in muscle force and motor function. Changes in muscle quality and function, especially in lower limbs, are crucial, as they expose individuals to increased risk of falls. To elucidate some of the related neuromuscular mechanisms, we investigated cortical inhibition and peripheral muscle twitch force potentiation in women during the early and late stages of perimenopause.

Methods: Participants were 63 women aged 48–55 years categorized as early (EP, n = 25) or late (LP, n = 38) peri-menopausal according to serum follicle-stimulating hormone (FSH) levels and menstrual diaries. EP women had an irregular menstrual cycle and FSH < 25 IU/L, while LP women had an irregular cycle and > 25 IU/L. We examined motor evoked potential (MEP) and silent period (SP) elicited by transcranial magnetic stimulation (TMS), in the tibialis anterior muscle at 20%, 40%, and 60% of maximal voluntary contraction (MVC) levels, and twitch force potentiation in plantar flexors.

Results: EP group showed a longer SP duration in 40% MVC condition and larger motor evoked potential amplitude in 20% MVC condition compared to the LP group. No group difference was detected in twitch force potentiation; however, it correlated negatively with FSH levels. Other factors, such as age, height, body mass index, or physical activity did not explain group differences.

Conclusions: Our preliminary results indicate subtle modulation in both TMS-induced inhibitory and excitatory mechanisms and twitch force potentiation in women already in the late perimenopausal stage. This suggests that the reduction of estrogens may have an accelerating role in the aging process of neuromuscular control.

Keywords: Menopause, Follicle-stimulating hormone, Motor cortex, TMS silent period, Twitch force potentiation

Background

Menopausal transition, i.e. perimenopause, is characterized by a range of physiological changes caused by alterations in female hormone levels [1]. These changes expose women to an early decline in muscle quality and motor function [2, 3]. Together with changes in muscular properties, neurophysiological and cortical mechanisms play a major role in motor deficits related to the normal aging process [4, 5]. As changes in muscle function and motor control especially in lower limbs expose individuals to increased risk of falls [6, 7], understanding alterations both in muscle function and cortical control is increasingly important. Female sex hormones have a strong neuroprotective role and reduction of estrogens during menopausal transition is associated with multiple

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Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 2 of 10

neurophysiological changes, such as neuroinflammation, mitochondrial dysfunction, and synaptic decline [8, 9]. While menopause is recognized as a reproductive transition, yet a variety of neural changes are known to occur, and several perimenopausal symptoms are mainly neurological [1].

Transcranial magnetic stimulation (TMS) is a pain-free, non-invasive clinical and therapeutic tool widely used in research to study cortical excitatory and inhibitory mechanisms [10–13]. TMS-elicited silent period (SP) is used to study cortical inhibition and is detected as suppression of on-going activity in surface electromyogram (EMG) of a contracted muscle, following TMS-elicited motor evoked potential (MEP) [14, 15]. The physiology of SP is under debate, but the early part of the silent period is suggested to originate from spinal mechanisms and the later part from cortical and possibly overlapping spinal inhibitory mechanisms [12, 16]. SP is believed to represent gamma-aminobutyric acid (GABA) receptor-mediated inhibitory mechanisms [12]. Pharmacological studies suggest this inhibition arises mostly through type B receptors ($GABA_B$) [18, 19]. Despite inter-individual variability in SP durations, consistent SP modulation is found in various clinical conditions, such as multiple sclerosis and Parkinson's disease [20, 21].

GABAergic levels are shown to decrease in aging and possibly even more pronounced in aging women [22, 23]. Female sex hormones are known to influence excitatory and inhibitory mechanisms including the GABAergic system [24]. TMS-induced inhibitory mechanisms have been studied in the normal aging process. Aging effects on SP are not entirely clear, however, both a decrease and no change in SP duration have been found in older adults compared to young [4, 25, 26]. Another TMS technique, paired-pulse TMS, has revealed both lengthening and shortening in intracortical inhibition, believed to represent $GABA_A$ergic inhibition [27, 28]. Inhibitory and excitatory neuromuscular mechanisms have not been studied during the menopausal transition, despite the changes in muscle function and force production. As menopausal transition seems to accelerate the changes observed during the normal aging process, corticospinal inhibitory mechanisms may demonstrate this modulation early on and thus are of interest in the study of menopause.

Force potentiation is a phenomenon in skeletal muscles, where produced force is temporarily enhanced by recent muscle activity [29, 30]. Twitch force potentiation is induced by peripheral electrical stimulation before and after conditioning voluntary muscle contraction. The mechanism behind muscle twitch force potentiation is believed to be phosphorylation of myosin regulatory light chains (pRLC), which makes actin and myosin more sensitive to Ca^{2+} and alters the structure of the myosin head [31]. Another suggested mechanism for force potentiation is the increase in recruitment of higher-order motor units [29]. Twitch force potentiation is shown to be lower in older adults and, interestingly, decreases have been observed already in women aged 45–54 years, about the same age as menopause [32–34]. Estradiol is previously connected to modulation of force potentiation mechanisms and myosin pRLC in mice [35]. Furthermore, Finni et al. [36] found higher twitch torque in postmenopausal women who were users of estrogen-containing hormone replacement therapy (HRT) compared to their monozygotic co-twins, who had never used HRT, without a difference in voluntary force generation. This suggests that modulation of involuntary force generation may be an initial indicator of decline in muscle force in postmenopausal women.

Menopause exposes women to an early decline in physical function and muscle force [2, 3]. The ability to perform coordinated movements in normal daily living relies on inhibitory and excitatory control. So far, neuromuscular mechanisms have not been investigated in menopausal women. In the present study, we investigated if both TMS-induced SP and peripheral twitch force potentiation are modulated in early and late perimenopausal women, with the changes in hormonal levels already present. The authors hypothesized a modulation in TMS-induced corticospinal inhibitory mechanisms, possibly seen as a shortening of SP, due to changes earlier observed in the aging population [25, 26]. As earlier research shows the modulation in twitch torque in postmenopausal women and modulation of pRLC due to changes in estradiol levels, we also hypothesized a decrease in twitch force potentiation [35, 36]. We recorded neuromuscular data and lower limb functional abilities from 63 women in the early and late stages of perimenopause. We chose lower limbs as our target because of their important role in functional abilities and balance maintenance during the aging process.

Methods

Study protocol

The participants were 63 women aged 48–55 (mean 51.4) years, a representative subgroup of the study population of the Estrogen Regulation of Muscle Apoptosis (ERMA) –project organized at the Gerontology Research Center (GEREC) and the Faculty of Sport and Health Sciences at University of Jyväskylä [37]. The complete ERMA-study protocol, including the current sub-study, was approved by the ethics committee of the Central Finland Health Care District (K-SSHP Dnro 8U/2014), Jyväskylä, Finland. The initial study population was randomly selected from the Finnish National Registry, kept

Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 3 of 10

by the Population Register Centre, targeting women aged 47 to 55 years living in the Jyväskylä area. An invitation letter with a prequestionnaire and general consent was sent to 6,878 women, from whom 46.9% responded. A total of 1,627 participants, fitting the inclusion criteria and consented, were invited to the laboratory visit. During the visit, a structured health interview was assessed, fasting blood samples were collected, and participants filled an informed consent for the subsequent phases of the ERMA study. Participants also kept a menstrual diary for at least 12 weeks. Exclusion criteria included estrogen-containing hormonal preparations or other medications affecting ovarian function, current pregnancy or lactation, conditions affecting ovarian function, including bilateral oophorectomy, body mass index (BMI) > 35 kg/m^2 (based on self-reported height and weight), and chronic diseases or medications seriously affecting muscle function. If a participant reported serious or unclear health problems, they were examined by a physician to ensure safe participation in physical performance tests.

The core-ERMA group used in the current study consists of women who had natural reproductive status, i.e., they had an intact uterus and they had not used during the past three months or were not currently using any hormonal contraception or other medication that could affect following up their menstrual bleeding pattern [37]. Menopausal status was determined by measuring participant's follicle-stimulating hormone (FSH) level from a blood sample taken, if possible, during the first five days of the menstrual cycle and by recordings in the menstrual calendar kept for six to twelve months. Also, each participant's 17β-estradiol (E2) levels were measured. FSH and E2 were detected with immunoassay using IMMU-LITE 2000 XPi (Siemens Healthcare Diagnostics, UK). All participants who took part in the current study with electrophysiological measurements were perimenopausal, without hormonal contraception, and with an intact uterus. Their perimenopausal status was further defined following Stages of Reproductive Aging Workshop guidelines [38] defined as *early perimenopausal (EP)* if FSH was below 25 IU/L and irregular menstrual cycle was reported and *late perimenopausal (LP)* if FSH was over 25 IU/L. Women with FSH over 30 IU/L and no menstrual bleeding during the past three to six months were considered postmenopausal and thus they were excluded from the current study. In addition, women with FSH below 17 IU/L and reporting regular menses were considered premenopausal and thus they also were excluded from the current study. The first three months of menstrual cycle length, the number of bleeding days, and the number of non-bleeding days were calculated for each participant. Three participants from the EP group and four from the LP group did not report any bleeding days during this time.

Women defined to be perimenopausal with a natural hormonal cycle were invited to take part in a subset of functional tests. Ninety-one women volunteered. Researchers performing the measurements and data analysis were blinded to participant's menopausal status and other background information. Good quality electrophysiological data were obtained from 63 participants, from which 25 were EP and 38 were LP (Fig. 1).

Functional measurements

Physical activity (PA) level was determined by the seven-point scale for the current level of weekly leisure-time PA [39]. The scale was previously shown to correlate well with accelerometer-based PA and mobility variables [40]. Questionnaire response categories were: (0) inactive, (1) light activity 1 to 2 times per week, (2) light activity several times per week, (3) moderate activity 1 to 2 times per week, (4) moderate activity several times per week, (5) high activity several times per week, and (6) competitive sports and related training several times per week. Categories 0 and 1 were further combined to low activity group, 2 and 3 to moderate activity group, and 4, 5, and 6 to high activity group.

Maximal isometric knee extension strength was measured in Newton-meters (Nm) in one leg, dominant hand side, with a Good Strength -dynamometer chair (Metitur Oy, Jyväskylä, Finland). The participant's knee was set at 60° angle from full extension and the ankle was strapped to force transducer. The participant was instructed to extend the knee with maximal force with verbal encouragement. The best performance of three to five isometric extensions was selected for the analysis.

Vertical jumping height was measured three to five times utilizing a contact mat. The jumping height indicates the participant's ability to elevate the body's center of gravity during a vertical countermovement jump. Flight time (t) was measured, and vertical jumping height (m) was calculated: $(g \times t^2) / 8 \times 100$[25]. The highest value was selected for the analysis.

Electrophysiological measurements were performed on the participants' right leg, while she sat in an ankle dynamometer chair, custom made in the University of Jyväskylä [41], with her back and head resting against the backrest. The knee was extended at 180 ° and the foot was strapped against the footplate at a 90 ° angle. Two surface electrodes (Ambu® BlueSensor N, 22 × 28 mm, Ballerup, DK) were placed on tibialis anterior (TA) and medial gastrocnemius (MG) muscles for bipolar EMG recording, with a 20 mm interelectrode distance and a ground electrode placed proximally.

Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 4 of 10
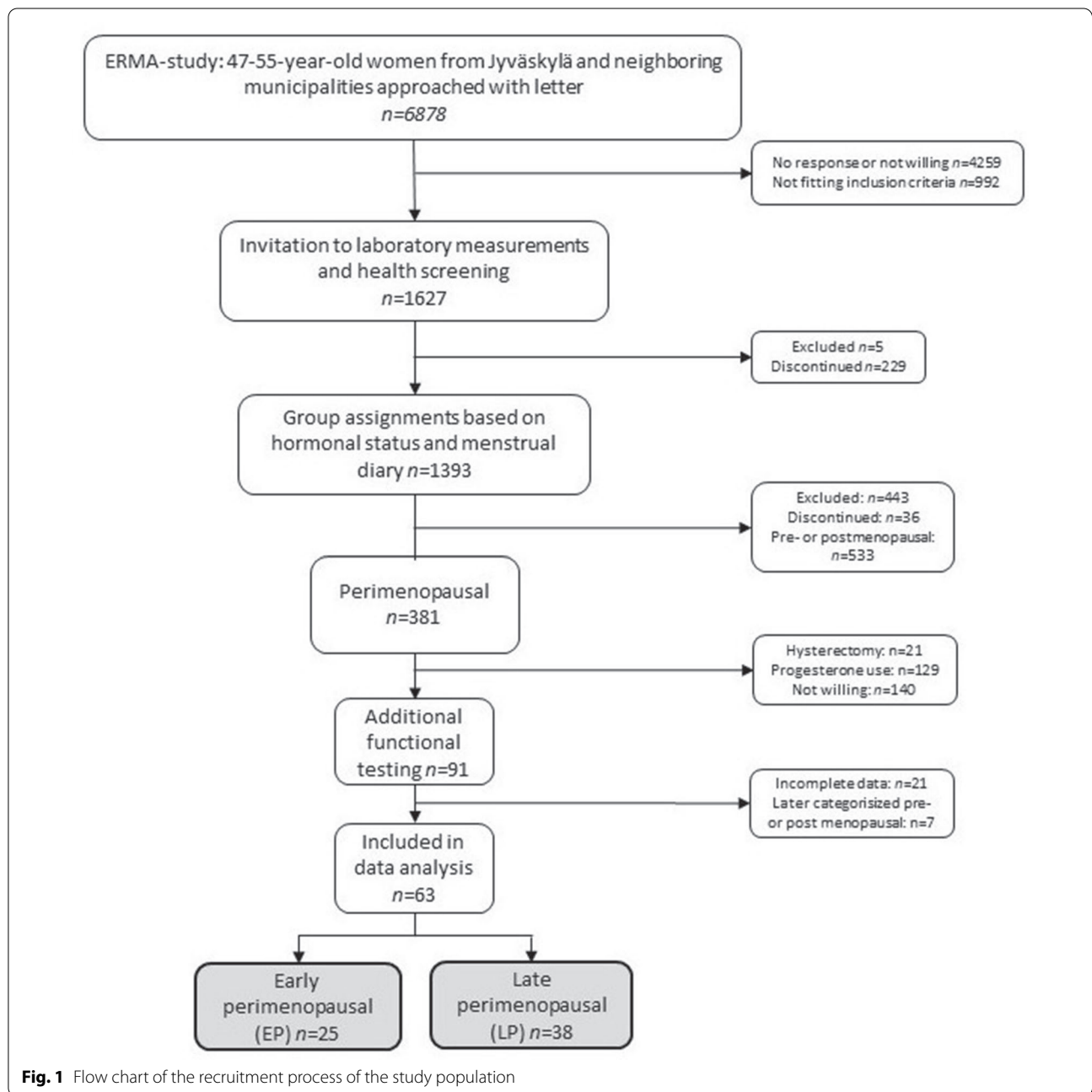
Fig. 1 Flow chart of the recruitment process of the study population

Before TMS procedures, maximal voluntary contraction (MVC) torque for ankle dorsiflexion was determined. MVC was defined as the highest torque from two maximal dorsiflexion contractions and 20%, 40%, and 60% of MVC were calculated. TMS was performed with Magstim Rapid[2] stimulator (Magstim, Whitland, UK) using a double 70 mm coil (figure-of-eight coil). Single-pulse stimulation was applied on the motor cortex over the measured and marked center of the scalp, with a 45° angle from the mid-sagittal lane to target the lower limb representation area on the contralateral hemisphere. Stimulation intensity was increased gradually to find the "hotspot" and assess the resting motor threshold (RMT). Individual RMT in the lower limb was set to the occurrence of 50 µV MEP in relaxed TA consecutively three times. Since the lower limb motor cortex locates deep in the central sulcus and may need relatively strong stimulus intensity to elicit MEP, we recorded the used stimulator output for each participant to control for its possible effects. This individual stimulation intensity was used

while the target muscle was contracted. Participants were instructed to perform isometric dorsiflexion at 20%, 40%, and 60% of their MVC, with rest periods in between. Such submaximal force levels are recommended e.g. by Säisänen et al. [14], as they are relatively easy to maintain during measurement. Produced force and the target force level were shown on the screen in front of the participants. The contraction was held continuously, while 6 to 10 stimulations were delivered at the individual hotspot with 10-s inter-stimulus intervals.

For twitch force recording, peripheral electrical stimulation was delivered to the tibial nerve in the popliteal fossa. The optimal stimulation point was located while the participant was lying prone. Gradually increasing stimulation intensity optimal location and intensity were defined where the peak-to-peak amplitude of the M-wave in the MG muscle and the configuration of the M-wave was repeatable for a minimum of three times. The cathode (Ambu® WhiteSensor 4500 M, 79 mm², Ballerup, DK) electrode was placed in this location and the anode electrode (V-trodes; Mettler Electronics, Anaheim, CA, USA) was placed slightly proximal to the patellofemoral joint. Supramaximal electrical stimulation of 1 ms duration, with 150% intensity of individual maximal M-wave, was delivered with a constant current stimulator (DS7AH, Digitimer Ltd., Hertfordshire, UK). The participant was then seated in the dynamometer chair and instructed to relax, while the first stimulus was delivered, and after that to perform a maximal isometric plantar-flexion, during which the second stimulus was delivered. After 2–5 s relaxation, the third stimulus was delivered to a relaxed muscle. Participants received verbal encouragement to perform the contraction and visual feedback of their torque level from the screen. Three trials including three stimulations were performed with 60-s rest intervals in between.

EMG signals were amplified $1000 \times$ and band-pass filtered (10 Hz–1 kHz). The ankle MVC was measured with a torque-transducer (Kistler Group, Switzerland), mounted between the ergometer servomotor and the platform of the foot.

Data analysis

For TMS data, individual MEP and SP responses were analyzed manually (Spike2 version 6.17, Cambridge Electronics Design, Cambridge, UK). MEP-start was detected as the point where the TA EMG signal exceeded baseline activity and the MEP-end as the point where the complete EMG silence began. This same time-point was also the SP-start. MEP amplitude was determined as the largest peak-to-peak amplitude. SP-end was where baseline EMG activity returned. For statistical analysis, both "absolute" SP duration (SP-start – SP-end) and "relative" SP (MEP-start – SP-end) were recorded [14, 42]. If a participant had four or more successful MEPs and SPs in one force level, those with the shortest and longest durations were not included in further analysis. From the remaining recordings, mean values for SP and MEP for each participant were calculated for each force level.

The electrical stimulation data were analyzed using Matlab (R2015a, 8.5.0, Mathworks Inc., Natick, MA, USA). Peak twitch torque (PTT) and maximal voluntary contraction (MVC) torque were manually detected from the torque signal (Fig. 2). Twitch force potentiation was analyzed by comparing PTT of pre-MVC twitch peak amplitude to post-MVC twitch peak amplitude in the recorded three trials using the equation: twitch potentiation (%) = ((post-MVC PTT/pre-MVC PTT)/pre-MVC PTT) × 100. The best potentiation effect and the best result from MVC out of three trials were selected for further analysis.
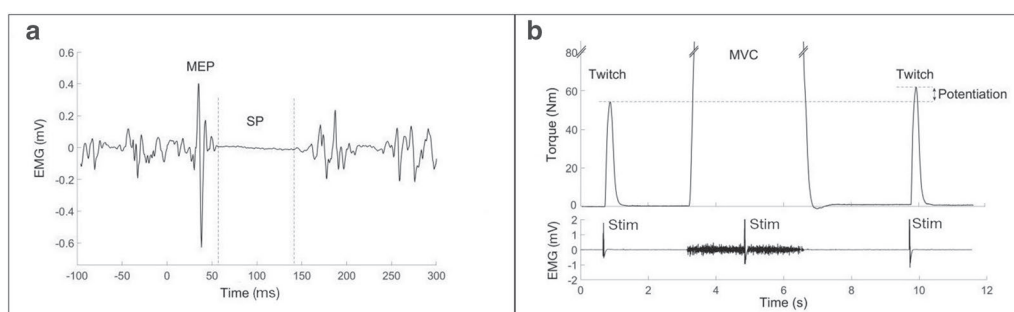
Fig. 2 A. EMG recording of TMS response from a single participant at 40% MVC condition in tibialis anterior muscle. Dashed lines indicate the start and end of SP. MEP amplitude was calculated as the maximum peak-to-peak amplitude. B. Torque data of twitch force potentiation analysis is presented from a single participant. Potentiation was calculated as the difference between pre-MVC twitch and post-MVC twitch. Stimulus artifacts are detectable in the EMG recording from the medial gastrocnemius muscle

Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 6 of 10

Statistical analysis was performed with IBM SPSS Statistics Version 24 (IBM Corporation, Chicago, IL, USA). Group comparisons between EP and LP women were performed with independent samples t-tests and for PA variable with chi-square test. Variability between different stimulation conditions was tested with paired-sample t-test. Correlations were detected with Pearson correlation coefficient or ANOVA. Covariance was tested with ANCOVA. The significance level was set to $p < 0.05$.
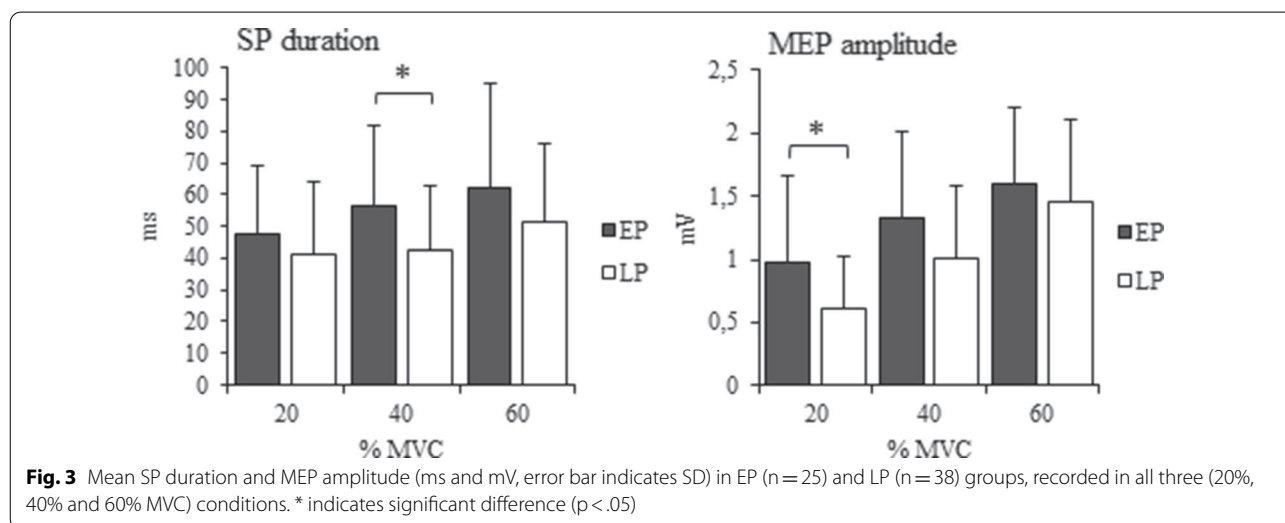
Results
Group characteristics
Both groups were approximately the same age, height, and BMI (see Table 1). As expected, the EP group had lower FSH levels and higher E2 levels than the LP group as well as a shorter duration of the menstrual cycle for the first three months of the follow-up period. No differences were detected in PA habits between groups. Stimulus intensities varied across participants but there were no differences between groups.

Silent period
SP duration differed between EP and LP groups in 40% MVC condition (t(61) = 2.473, p = 0.016). Mean absolute SP duration for the EP group was 57.1 ± 25.8 ms and for the LP group 42.8 ± 20.1 ms. The difference remained after controlling for stimulus intensity (F(1,60) = 6.044, p = 0.017). There was no significant difference between groups in 20% MVC ($47.8 \pm 22.0/41.1 \pm 22.7$, t(61) = 1.156, p = 0.252) and 60% MVC ($62.2 \pm 33.6/51.3 \pm 24.5$, t(61) = 1.491, p = 0.141) conditions (Fig. 3). Duration of SP increased with required muscle force for all participants (p < 0.01). In EP group the increase in SP duration was significant from 20 to 40% MVC conditions (p < 0.01) and in LP group from 40 to 60% MVC conditions (p < 0.01) (Fig. 3).

When analyzing relative SP, it also differed between groups in 40% MVC condition (t(61) = 2.494, p = 0.015). Mean relative SP duration for EP group was 88.4 ± 29.4 ms and for LP group 72.1 ± 22.5 ms. No significant difference was found in 20% MVC (78.4 ± 25.6 ms/68.7 ± 25.5 ms, t(61) = 1.475, p = 0.145) or 60% MVC (93.2 ± 38.1 ms/80.9 ± 26.9 ms, t(61) = 1.507, p = 0.137) conditions.

Table 1 Characteristics of the participants, mean (± SD) or n (%)

	EP (n = 25)	LP (n = 38)	P-value
Age, y	51.0 (± 2.0)	51.6 (± 1.8)	0.222
Height, cm	163.8 (± 0.1)	164.2 (± 0.1)	0.810
BMI	25.4 (± 4.4)	25.3 (± 3.7)	0.916
FSH (IU/L)	17.32 (± 4.79)	48.25 (± 22.28)	< 0.001
E2 (nmol/L)	0.374 (± 0.257)	0.249 (± 0.200)	0.035
Mean cycle length	36.8 (± 22.2) [a]	65.8 (± 41.7)[b]	0.001
Mean bleeding days	6.0 (± 1.4) [a]	5.3 (± 1.5)[b]	0.098
Mean non-bleeding days	34.7 (± 31.6) [a]	65.2 (± 49.1)[b]	0.006
Physical activity			0.652
Low	4 (16)	6 (16)	
Moderate	7 (28)	7 (18)	
High	14 (56)	25 (66)	
Stimulus intensity (%)	83.6 (± 7.7)	84.5 (± 9,6)	0.691

P-values tested with independent samples t-test, physical activity level with chi square test. BMI = body mass index, cm = centimeter, E2 = 17β-estradiol, FSH = follicle-stimulating hormone, IU/L = international units per liter, nmol/L = nanomoles per liter, SD = standard deviation, y = year. [a]n = 23, [b]n = 34.

Fig. 3 Mean SP duration and MEP amplitude (ms and mV, error bar indicates SD) in EP (n = 25) and LP (n = 38) groups, recorded in all three (20%, 40% and 60% MVC) conditions. * indicates significant difference (p < .05)

Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 7 of 10

Motor evoked potential

MEP amplitude differed between groups in 20% MVC condition (t(61) = 2.511, p = 0.017). EP group mean amplitude was 1.000 ± 0.688 mV and for LP group 0.617 ± 0.409 mV. The difference remained when controlling for stimulus intensity (F(1,60) = 7.460, p = 0.008). MEP amplitudes showed a similar tendency in 40% MVC condition, as mean amplitude was 1.326 ± 0.707 mV in EP group and 1.010 ± 0.576 mV in LP group (t(61) = 1.944, p = 0.057), albeit not significant. There was no significant difference in MEP amplitudes in 60% MVC condition (1.598 ± 0.607 mV/1.454 ± 0.648 mV, t(62) = 0.883, p = 0.381). MEP amplitude increased with muscle force in both groups (p < 0.001).

Absolute SP duration and MEP amplitude correlated in 40% MVC condition (r = 0.260, p = 0.040) (Fig. 4) and 20% MVC condition showed similar tendency, but not significant (r = 0.235, p = 0.063). No correlation was found between SP duration and MEP amplitude in 60% MVC condition (r = 0.077, p = 0.548).

Twitch force potentiation and physical performance

Twitch force potentiation did not differ between groups. An association between twitch force potentiation and FSH (r = -0.262, p = 0.043) was observed. No association was found between twitch force potentiation and E2 (r = 0.123, p = 0.348). There were no differences between groups in vertical jumping height, knee extension strength, or ankle dorsiflexion strength (Table 2). However, EP group had 17.2% stronger plantar flexion compared to LP group (t(57) = 2.533, p = 0.014). There was no correlation between plantar flexion torque and SP duration in 40% MVC condition (r = 0.029, p = 0.830) nor

Table 2 Measures of lower limb physical performance and twitch force potentiation, mean ($\pm$ SD)

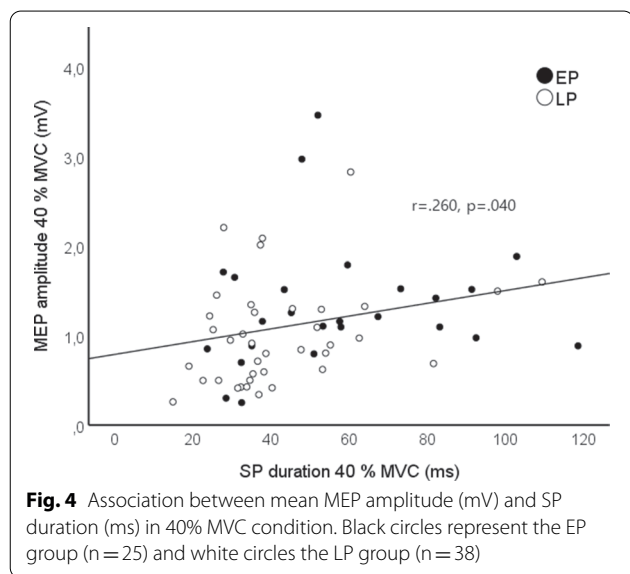|	EP (n = 25)	LP (n = 38)	P-value
MVC dorsiflexion (Nm)	31.9 ($\pm$ 9.1)	34.3 ($\pm$ 6.7)	0.238
MVC plantarflexion (Nm)	131.1 ($\pm$ 33.9)[b]	108.8 ($\pm$ 32.4)[b]	0.014
Knee extension strength (Nm)	162.2 ($\pm$ 27.9)[b]	153.7 ($\pm$ 38.8)[c]	0.360
Vertical jumping height (m)	0.185 ($\pm$ 0.046)[a]	0.200 ($\pm$ 0.037)[a]	0.177
Twitch force potentiation (%)	10.1 ($\pm$ 6.3)[a]	6.7 ($\pm$ 9.3)[b]	0.124

P-values tested with independent samples t-test. MVC = maximal voluntary contraction, m = meter, Nm = Newton meter, SD = standard deviation.
[a] n = missing one, [b] n = missing two, [c] n = missing five.

with plantarflexion torque and MEP amplitude in 20% condition (r = 0.130, p = 0.327).

Discussion

The aim of the present study was to examine TMS-induced inhibition and peripheral twitch force potentiation in women in early and late perimenopausal stages, to determine if the progression of the menopausal stage affects motor control mechanisms. Our finding was that women in the EP group presented longer SP durations than women in the LP during a moderate force production condition (40% MVC). MEP amplitudes were sensitive to the perimenopausal stage as in 20% MVC condition EP group showed larger MEP amplitudes and the same tendency remained in 40% MVC condition. Furthermore, an association was observed between twitch force potentiation and FSH. Our participants were comparable in age, height, BMI, and PA level and thus those factors do not explain the differences we detected.

Our results indicate a reduction in corticospinal inhibitory mechanisms observable already in late perimenopause. While pharmacological studies have provided strong evidence for GABAergic origins of SP [17–19, 43], there remains a debate over the spinal and cortical contribution to the generation of SP. Formerly, the early part ($\sim$ 50 ms) of SP has been thought to arise from spinal origins and the later part from cortical origins [16–19, 42, 44]. Recently Yacyshyn et al. [45] suggested that spinal inhibitory mechanisms could play an even larger role in SP generation than previously thought. They found cervicomedullary motor evoked potential suppression at up to 150 ms after TMS. However, as long-lasting cortical GABAergic neurons probably affect SP throughout its duration, it is unclear how the spinal and cortical inhibitory mechanisms interact in the latter part of the SP. Further studies are needed to determine their roles in SP generation.

Fig. 4 Association between mean MEP amplitude (mV) and SP duration (ms) in 40% MVC condition. Black circles represent the EP group (n = 25) and white circles the LP group (n = 38)

During aging, competencies indicating good motor coordination and performance are important, as they reflect an individual's overall motor abilities and the risk of falls [6, 7]. This association is further emphasized in aging women, as menopause exposes them to early decline of muscle function [2, 3]. TMS studies indicate a strong cortical contribution in controlling muscle activity e.g. during the gait cycle, that can be modulated by intra-cortical inhibition [46]. There is also growing evidence that older individuals utilize somewhat different cortical mechanisms in motor control tasks compared to young [47, 48]. Along with decreasing levels of GABA [22, 23], decreased inhibition has been observed in older adults, and it has been connected to decreased control of coordinated movements [25, 26, 49, 50]. Recently, Swanson and Fling [50, 51] reported shorter SP in older adults than young. Older adults also demonstrated an association between shorter SP and reduced performance in walking and turning, while an opposite correlation was observed for young adults. This was only present in the right hemisphere stimulation. The results suggest that decreased inhibitory control may underlie age-related decline in motor control and coordination. Our results offer a proposal that changes in hormonal levels in menopausal transition may accelerate the decrease in inhibitory mechanisms in cortical or spinal levels and possibly accelerate the aging process of motor function. Unlike the study by Swanson & Fling [50], we performed the stimulation only to the left hemisphere, where they did not find significant differences between young and older adults. Therefore, we cannot make further conclusions about hemispheric differences.

Furthermore, we found lower MEP amplitude in LP than in the EP group indicating modulation of cortical excitability in perimenopausal stages. Reduced MEP amplitudes in older adults compared to young are a common finding, and our results suggest that menopause may accelerate this modulation [25, 26, 49]. Here, SP durations and MEP amplitudes were associated in moderate force production condition. This relationship between SP and MEP has been previously reported [14, 25, 52]. Therefore, the mechanisms that underlie the changes observed in SP and MEP, may have similar origins.

Twitch force potentiation did not differ between EP and LP groups. However, there was a negative correlation between participants' FSH level and twitch force potentiation. This correlation suggests modulation toward decreasing twitch force potentiation in the menopausal transition. FSH level fluctuates also during menstrual cycle in women. However, no association has been found earlier with involuntary muscle contractile properties and FSH levels during menstrual cycle [53]. A correlation was not present with E2 but only with FHS, which

may be more sensitive here to different stages of perimenopause. Furthermore, the very subtle fluctuations of E2 may not be detected with IMMULITE 2000 XPi. Twitch force potentiation and twitch torque have been shown to decrease in aging women and are suggested to partly underlie the morphological and functional changes observed in aged muscle [33, 36]. As estradiol seems to modulate force potentiation mechanisms [35], it may be that the twitch force potentiation deteriorates in menopausal women, but this modulation was not large enough to be yet detected between the perimenopausal stages in the present study.

There were no differences between groups in knee extension strength, vertical jumping height, or ankle dorsiflexion strength. Our results suggest that these functional measures are not yet sensitive for a decline in present perimenopausal stages. Nevertheless, plantar flexion strength was higher in EP group than LP group and may point toward early modulation in muscle function in menopause. it should be noted that the decrease in hormonal levels in menopause is a risk factor for sarcopenia. It seems that the late perimenopausal stage does not yet reveal evidence for a decrease in muscle strength and function, although direction toward it may be observed [54].

This study has several limitations. Our sample size is relatively small, and the observed interactions should therefore be investigated in larger samples. TMS stimulation was performed without advanced navigation and information on individual brain images. Leg motor areas are relatively small, located deep in the inter-hemispheric fissure and the optimal stimulation points are less segregated than those of hand muscles [55]. Therefore, it can be challenging to find the optimal stimulation point and higher intensities may be required to elicit measurable MEP compared to hand [56]. For this, we used a stimulus intensity that was the individually detected lower limb RMT for each participant. This may provide a challenge for generalization, as different levels of stimulation intensities have resulted in different results in research. E.g. changes in SP after fatiguing exercise have been detected at lower TMS intensities but not at higher intensities [57]. It might be that the changes detected here are present at low stimulus intensities but not with higher ones. However, this requires further investigation. As the detection of RMT and SP may be challenging for the lower limb and older participants, we controlled our results for the intensity of the stimulator output. Furthermore, the number of TMS trials to achieve each MEP and SP average was rather small [12, 58]. Unlike the study by Swanson & Fling [50], we performed the stimulation only to the left hemisphere, where they did not find significant differences between young and older adults. Therefore,

Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 9 of 10

we cannot make further conclusions about hemispheric differences. Thus, our preliminary results require further investigation.

Our method to measure very low E2 levels with IMMULITE 2000 XPi has some inaccuracy, and thus the most subtle fluctuations may not be revealed. Therefore, all associations may not have become apparent. Our results of E2 levels were in line with FSH levels and menstrual histories. Our study participants did not include pre- or postmenopausal women; thus, we cannot draw inferences of how the detected modulation in inhibitory or excitatory processes relates to either the fertility stage or the postmenopausal stage.

Conclusions

Our preliminary results indicate subtle modulation toward decreasing TMS-induced inhibition in the central nervous system and possibly decreasing muscle twitch force potentiation in perimenopausal women. Faultless interaction of inhibitory and excitatory processes is essential in appropriate motor control and our results suggest that the reduction of estrogens in menopausal transition may accelerate the aging process related to this interaction.

Abbreviations

ANOVA: One-way analysis of variance; ANCOVA: Analysis of covariance; BMI: Body mass index; E2: 17β-Estradiol; EMG: Electromyography; EP: Early perimenopausal; FSH: Follicle-stimulating hormone; GABA: Gamma-aminobutyric acid; LP: Late perimenopausal; MEP: Motor evoked potential; MG: Medial gastrocnemius; MVC: Maximal voluntary contraction; Nm: Newton meters; pRLC: Phosphorylation of myosin regulatory light chains; PA: Physical activity; PTT: Peak twitch torque; RMT: Resting motor threshold; SD: Standard deviation; SP: Silent period; TA: Tibialis anterior; TMS: Transcranial magnetic stimulation.

Authors' contributions

EL, VK, SS, TF and IMT conceived and designed research. HP, EL, PH and SS performed experiments. HP, EL, PA, SS and TF analyzed data. HP, EL, PA, TF and IMT interpreted results of experiments. HP prepared figures and drafted manuscript. HP, EL, PH, PA, VK, SS, TF and IMT edited and revised manuscript. All authors approved final version of manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The complete ERMA-study protocol, including the current sub study, was approved by the ethics committee of the Central Finland Health Care District

(K-SSHP Dnro 8U/2014), Jyväskylä, Finland. All participants filled an informed consent for the complete ERMA study and subsequent phases.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Pesonen *et al. BMC Women's Health*   (2021) 21:133

Page 10 of 10

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II

TEN-YEAR RESISTANCE TRAINING BACKGROUND MODULATES SOMATOSENSORY P3 COGNITIVE BRAIN RESPONSE IN OLDER MEN: A MAGNETOENCEPHALOGRAPHY STUDY

by

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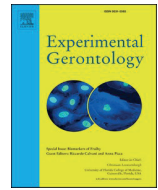
Ten-year resistance training background modulates somatosensory P3 cognitive brain resonse in older men: A magnetoencephalograpy study

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ARTICLE INFO

ABSTRACT

The brain electrophysiological component P3, associated with good cognitive abilities, deteriorates during healthy aging. Both cognitive functions and P3 component amplitude respond positively to exercise, but the effects of resistance training on P3 are much less studied. Short-term resistance training interventions in older adults indicate modulation towards larger P3 amplitude, but this association has not been studied with a longitudinal study design. We investigated magnetoencephalographically recorded P3 (P3m) in a unique study design of nine aged men (mean age 77.7 y) with quasi-supervised resistance training background over a 10-year period and eight controls of similar age (mean age 77.5 y) with no training background. We elicited P3m utilizing lower limb electrical stimulation, as the resistance training program was mostly directed to lower limbs. Somatosensory oddball paradigm was performed with the right foot's fourth toe as standard (90%) and hallux as deviant (10%). Participants were asked to respond to deviants with a button press using their left index finger. Topographic maps showed bilateral temporoparietal activation for P3m in both groups. No amplitude differences were found in active P3m regions between groups. However, the groups differed in hemispheric activity of P3m. The exercise group showed stronger activation in the right frontotemporal and parietal sensor-groups compared to the left sensor-groups, and the control group showed stronger activation in right frontotemporal sensor-group compared to left. The control group showed shorter P3m latency in the right temporal sensor-group than the exercise group, but the latencies in other sensor-groups were similar. In aging, the brain utilizes compensatory areas to perform cognitive tasks. Our results suggest modulation in topographic distribution of P3m activity in aging men with long-term resistance training background compared to their controls. This might arise from a difference in age-related compensatory mechanisms in P3m generation.

1. Introduction

In normal aging, the brain undergoes both structural and functional changes, leading to a decline in cognitive performance in late life (Beheshti et al., 2019; Harada et al., 2013). Cognitive abilities such as memory, processing speed, attention, and executive functions, are among those subjected to age-related deterioration, especially after the age of 60 (Harada et al., 2013; Reuter-Lorenz and Park, 2010). Event-related potential P3 (previously called P300) is a widely studied brain electrophysiological component as a measure of cognitive function. Specific brain processes behind P3 generation remain elusive and it likely originates from several overlapping cognitive processes. P3 is linked to attentional processes, memory, and executive function, and it

is reliably elicited with an oddball paradigm demanding conscious detection of random target stimuli (Polich, 2007; van Dinteren et al., 2014). P3 is also sensitive to the effects of aging. Reduced P3 amplitude, altered topographic distribution of brain activity, and longer P3 latency are reported to occur in older individuals compared to young (Polich, 1996; van Dinteren et al., 2014). Thus, it serves as a useful tool to study age-related deterioration in brain function.

So far, P3 has been mostly studied with electroencephalography (EEG). It is reliably detected as a centroparietal cortical electrophysiological component, a positive waveform, approximately 300 ms after the target stimulus onset. P3 represents complex brain functions involving target detection, memory, and decision-making. Recognizing individual sources has proven difficult, and it is considered to originate from many

independent sources and their broad and deep connections in the brain (Polich and Kok, 1995; Polich and Criado, 2006). Studies using EEG and magnetoencephalography (MEG) methodologies have detected bilateral temporoparietal, medial temporal and frontal sources for somatosensory P3 (Rezaie et al., 2011; Tarkka et al., 1996; Valeriani et al., 2001). Furthermore, lesions in the temporoparietal junction have been shown to markedly reduce P3 for both lower and upper limb somatosensory stimulation (Yamaguchi and Knight, 1991; Yamaguchi and Knight, 1992).

During aging, physical activity is an important lifestyle element to maintain physical and cognitive health (Hamer et al., 2014; Harada et al., 2013; Northey et al., 2018). Research also indicates a strong connection between exercise and higher P3 amplitude in the aging brain. Yet, most P3 research has focused on aerobic exercise, fitness, and physical activity background (Kao et al., 2019; Pontifex et al., 2009; Strömmer et al., 2017). Resistance training is a promoted exercise method for older adults, as it maintains functional capacity and good quality of life (Fragala et al., 2019; Ihalainen et al., 2019; Kell et al., 2001; Walker et al., 2014). It has also been demonstrated to improve cognitive functions during aging (Northey et al., 2018). Studies have investigated whether improvement in cognitive function can be observed also in P3 characteristics. Özkaya et al. (2005) reported higher P3 amplitudes in older individuals after a 9-week resistance training intervention, and Tsai et al. (2015) reported diminished amplitude in non-training controls but not in resistance-trained individuals after 12 months of training (mean age 75.8 and 70.9 y, respectively). Resistance

training interventions could help to attenuate age-related deterioration seen in P3 component. However, there is insufficient evidence to conclude whether this effect is seen after years of resistance training. Furthermore, short-term interventions may provide multiple other beneficial aspects for brain and cognition, such as learning new skills and social activity, compared to years of training. As cognitive decline in healthy aging develops slowly, and it seems that longer training interventions have shown more consistent results in improved cognition compared to shorter interventions (Saez de Asteasu et al., 2017), it is yet to be shown whether long-term resistance training consistently effects P3 characteristics.

In the present study, we examined magnetically recorded P3 (P3m) elicited with lower limb stimulation, a unique quasi-experimental study design in healthy older men. We have tracked the resistance training and strength performance of (presently) ~77-year-old men over ten years along with controls of similar age who have no regular training background. We chose lower limb stimulation as our target because of the critical role of lower limbs in an individual's functional capacity and independence, and the resistance training program included exercises targeting lower limb muscles. We hypothesized that there would be modulation in P3m towards larger amplitudes in older men with a long-term resistance training background.
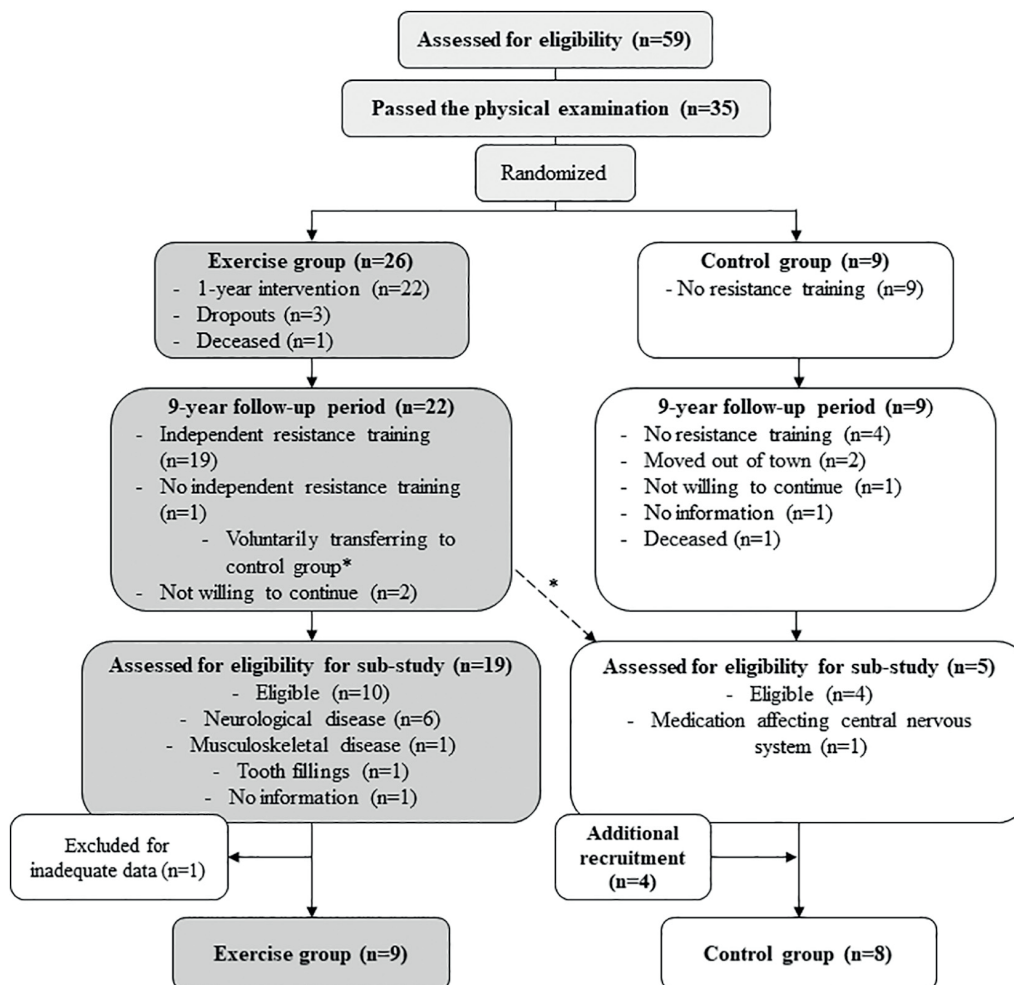

Fig. 1. Flow chart describing the flow of the participants during the 10-year study process.

2. Materials and methods

2.1. Participants

Participants were 17 male volunteers; age range from 74 to 82 years. The exercise group consisted of nine men aged 77.7 $\pm$ 2.1 y, and the control group of eight men aged 77.5 $\pm$ 2.5 y (Fig. 1). This study was performed as a sub-study of a larger SARCOPENIA-project, started as a randomized trial in 2007 in the Faculty of Sport and Health Sciences, University of Jyväskylä (Ahtiainen et al., 2015).

Initially, a total of 35 men took part in a one-year supervised intervention study. Participants were recruited with an advertisement in the local newspaper and all volunteers went through detailed medical screening. All participants aged ~70 years, who passed the physical examination were included in the original study. Exclusion criteria were cardiovascular and pulmonary diseases, malfunctions of the thyroid gland, diabetes, obesity (body mass index $\geq$30), or any other disease or medications that may have precluded the ability to perform the exercise training and testing, and participation in systematic physical training in the previous year. After the baseline measurements, researchers performed block randomization by a random number generator to three resistance training groups, which differed only by muscle biopsy procedures in the measurements, and one control group (3:1 for exercise and control, but 1:1:1:1 for each original group). Twenty-six participants were randomly selected to the exercise groups with identical resistance training intervention and nine to the non-exercising control group.

The exercise group first participated in one-year supervised resistance training (two times a week for six months and then three times a week for six months) in the University gym. Exercises included leg press, squat, and knee extension and flexion for lower limb muscles, and four to five exercises targeting the other main muscles of the body. The training was first performed with light loads, seven to eight exercises at 40–60% of one repetition maximum (1RM) with three 10–20RM sets and short rest periods in between. After one month the loads were increased progressively up to 60–80% of the 1RM in three to five sets (8–12RM per sets) to increase muscle mass. After three months, 9 to 10 exercises were performed and the training program also included higher loads, 70–90% of the 1RM, with a longer recovery time, using 5–10RM sets to optimize gains in maximal strength. In the training program, two sets were also performed with lower loads (40–50% of the 1RM with 8–12 repetitions) and higher movement velocities to improve muscle power (Ahtiainen et al., 2015). After the first year, participants in the exercise group continued voluntary resistance training ~2 x week, without any supervision. The present control participants continued their normal daily routines without resistance training. Participants were followed up with strength measurements after the first and second years of voluntary training, and later after four and seven years. Participants kept a training diary during the year with supervised training and completed questionnaires for each follow-up measurement. During the first year, one participant from the exercise group died and three participants were not willing to continue with the study program. Two participants from the exercise group and one participant from the control group declined to participate in follow-up measurements. In addition, two participants from the control group moved to another region, one was not reached, and one was deceased. One participant in the exercise group did not continue resistance training after the first-year intervention and transferred voluntarily to the control group.

After ten years, 24 men participated in the follow-up measurements and were invited to the present sub-study. Six participants from the exercise group and one participant from the control group were excluded from MEG registration due to a diagnosis of neurological or psychiatric disease, such as Parkinson's or Alzheimer's disease or depression. From the exercise group, one participant was not measured due to tooth fillings, one for musculoskeletal issues preventing from participating in the MEG measurement, and one participant was not reached.

From the 14 participants taking part in the MEG recordings, 10 participants were part of the original exercise group and had continued self-directed resistance training until the 10-year follow-up. Mean $\pm$ SD training adherence for the first year was 93 $\pm$ 8% and participants reported 2.2 $\pm$ 0.4 resistance training sessions per week during the subsequent follow-up. One participant was later excluded from the exercise group for inadequate MEG data ($n = 9$). The control group of the present study consisted of four original participants and four recent recruits ($n = 8$) (Fig. 1). The inclusion criteria for the new recruits were; age 72 to 80 years, no background in resistance training or other regular moderate or vigorous exercise training, no neurological or psychiatric diseases or medications affecting the nervous system, or disease that prevents normal exercise training or daily activities, and no pacemaker or metal implants preventing the MEG registration. All original participants except one resistance trained and one control subject reported carrying-out endurance-type physical activities during the 10-year period, e.g., skiing, swimming, and walking. Participants in the exercise group reported remaining healthy for the follow-up period and being able to continue resistance training. One participant reported musculoskeletal disease that did not affect the exercise training. All control participants reported health-related changes during the follow-up period that did not prevent participating in MEG recordings. All recordings and analyses were performed blinded to the participants' group status.

2.2. Task and stimulation procedure

We performed a somatosensory oddball task utilizing electrical stimulation (DeMeTec SCG30, DeMeTec GmbH, Langgöns, Germany) delivered to the fourth toe and hallux of the right foot. Two non-magnetic ring electrodes, built in-house, were placed proximally and distally on each toe (Fig. 2) with 1 cm inter-electrode distance. Five-hundred monophasic square-wave current pulse stimuli of 0.2 ms duration were delivered with an interstimulus interval of 1000 ms. Standard stimuli (90%) were delivered to the fourth toe and deviant stimuli (10%) to hallux. Stimulation intensity was set individually at 120–150% of the sensory threshold to a comfortable level with clear sensation without any pain and adjusted separately for each toe. Participants were instructed to attend to stimuli and react to each deviant stimulus in the hallux by pressing a button in a response box with their left index finger. All participants reported being right-handed.

2.3. MEG recording

Somatosensory evoked field recordings were conducted with 306 sensor magnetoencephalography equipment (Elekta Neuromag®, Triux™, Stockholm, Sweden) in a magnetically shielded room with a bandpass of 0.1–330 Hz and a sampling rate of 1000 Hz. Eye movements and blinks were recorded with electro-oculogram (EOG). To register head shape and position, five continuous current head position indicator (HPI) coils were placed on the scalp. Head shapes were registered with a 3D digitizer (Fastrak®, Polhemus, Vermont, USA) in addition to the nasion and preauricular points, along with circa 100 additional points around the scalp and nose. In MEG, participants were asked to sit still, with hands resting on the table (the left hand ready on the response box) and gaze fixed forward on a black dot approximately 1.5 m in front of them. They were advised to avoid blinking during the recordings. The head position was continuously monitored through the recording. The data were stored for offline analysis.
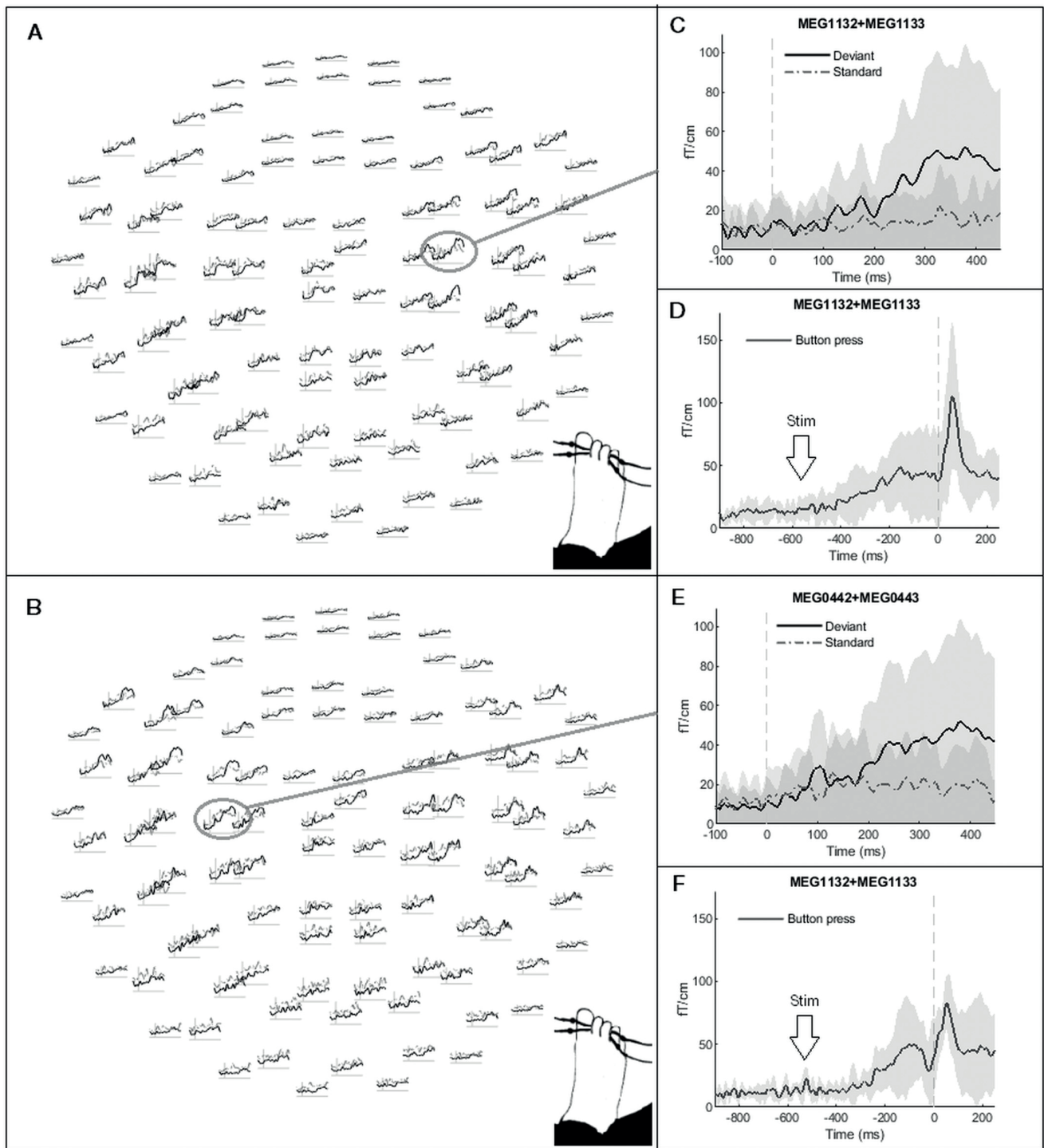
Fig. 2. Grand average waveforms (root sum squared, RSS) recorded from planar gradiometers showing both standard and deviant conditions superimposed. The exercise group is presented above (A) and the control group below (B). Stimulation electrode ring placement in the right foot is shown below waveforms. For both groups, a selected gradiometer pair with strong activity in the time window of 320–390 ms is shown in the right panels (C, E). Right panels (D, F) show one gradiometer pair averaged to the button press, selected based on the strong activity from the right hemisphere in the primary motor cortex area (M1), demonstrating both the readiness field before movement onset and the motor-evoked field peaking after the button press.

2.4. Data analysis

For preprocessing of data, temporal signal space separation (tSSS) (Taulu and Simola, 2006) with Maxfilter software (Elekta Neuromag®, Stockholm, Sweden) was utilized to reduce external artifacts and detect bad channels. The head position was transferred to mean coordinates for (maximum change of 2 cm) participants to enable group averaging and sensor-space analysis. After this, data were analyzed offline with Brainstorm software (version 29/3/2019). The data were bandpass filtered at 0.1–40 Hz. Eye blinks were detected from EOG traces. For

some participants, we detected blinks exceeding the absolute value of the filtered signal at least six times the standard deviation (SD) due to excessive blinking. Detected eye blinks were removed utilizing signal-space projection (SSP) (Uusitalo and Ilmoniemi, 1997). Raw data were manually inspected, and segments with artifacts from muscle tension were removed. Data were segmented to epochs from −100 to 450 ms in relation to the stimulus onset, with a baseline correction of −100 to −1 ms. A stimulation delay of 3 ms, identified from stimulus artifacts, was corrected. Deviant epochs and an equivalent number of standard epochs preceding a deviant were averaged separately for each subject. The maximum allowed reaction time for deviant identification was 0.999 s, and only those deviants correctly identified with a button press within this time limit were taken into analysis. The minimum number of accepted deviants per individual was 29, and the average number obtained for all participants was 43. One participant from the exercise group was excluded from the analysis for not having enough accepted epochs.

2.5. Group source analysis

First, all gradiometers and magnetometers were used for source analysis. As we had no individual MRI images, each participant's head shape was aligned to a default anatomy template ICBM152. Noise covariance analysis was calculated utilizing empty room measurements recorded before each participant's research visit. The source model was performed with overlapping spheres and averaged epochs were used to generate minimum norm estimate current density maps in Brainstorm software. Current density maps were normalized with Z-score transformation and finally spatially smoothed. Based on previous P3 studies (Tarkka and Stokic, 1998; Yamaguchi and Knight, 1992), regions of interest (ROIs) were investigated with Brainstorm scout function.

Grand average source maps were created by extracting current source density maps with absolute values and creating grand average source maps for each group. Grand average source maps were used to detect ROIs with maximum amplitude between 320 and 390 ms for the exercise group and the control group. Scouts with 40 vertices were created at the source with maximum amplitude for each group, and a matching one was created in the contralateral hemisphere. These were investigated for each participant using group average scout waveform peak as the temporal cue, resulting in different latencies of the peak amplitudes (324–330 ms for the exercise group, 382–388 ms for the control group). A maximum amplitude using the group-determined time window was detected in each participant's scout waveform to explore common activations and hemisphere differences.

2.6. Sensor-level analysis

Second, for single sensor analysis, only gradiometers were included in the analysis as they best represent the brain activity below a specific sensor. Each 102 gradiometer pair signals were combined by calculating their root sum square (RSS; sqrt(grad2^2 + grad3^2)) to control for the sign of the amplitude (Fig. 2). A similar method has been utilized previously (Kida et al., 2007; Onishi et al., 2013). The obtained gradiometer pair signals were used to locate the sensor with maximum amplitude from each participant between 320 and 390 ms, and peak amplitude and latency were measured. We also detected average amplitude within 320–390 ms time-period in order to measure average activation in typical P3 time-window because this activity involves larger processes and possibly deeper brain areas.

2.7. Sensor-group analysis

Third, information from topographic maps and gradiometer pair RSS waveforms with maximum activation was used to create sensor-groups from gradiometer pairs to detect activity from a broader area of cortex. As the magnetic fields showed bilateral temporal activity already

around 200–260 ms time-window, we measured both early deviant detection (M200) and P3m. Sensor-groups were formed for fronto-temporal (P3m), temporal (M200, P3m), and parietal (P3m) cortices similarly for both hemispheres, according to topographic maps. We used a time-window of 200–260 ms, detected from the grand average waveforms, for M200 response and the previously determined time-window 320–390 ms for P3m. M200 was detected from temporal sensor-groups, and peak amplitudes and latencies were recorded. For P3m, we detected peak amplitudes, peak latencies, and average amplitudes, measured from temporal, frontotemporal, and parietal sensor-groups.

2.8. Statistical analysis

Statistical analysis was performed with Brainstorm software and IBM SPSS Statistics Version 24 (Armonk, NY, USA). The normality of the data was tested with the Shapiro-Wilk test. All between-group comparisons were tested with independent samples t-test for normally distributed data and Mann-Whitney U test for the non-normal data. Normally distributed data are presented as means and standard deviations and non-normally distributed data as medians and interquartile ranges. P3m and M200 analysis in sensor-groups was performed using linear mixed model (group, hemisphere, group*hemisphere). One major outlier exceeding upper fence (Q3 + (1.5 * IQR)) was detected in P3m average amplitude difference scores in left and right temporal sensor-groups. Therefore, we performed an additional analysis, excluding the outlier, as a sensitivity analysis for this variable. Between-group differences in latencies were tested with Mann-Whitney U test for non-normally distributed data. P-values (2-tailed) are presented as exact and the statistical significance threshold was set to <0.05.

3. Results

3.1. Group characteristics

The groups were similar in their age, height, and weight. No between-group differences in reaction time or target hits were observed (mean 91 ± 4% for the exercise group and 83 ± 5% for the control group). All mean values are shown in Table 1.

3.2. Group source localization

Fig. 3 shows minimum norm estimate source maps for exercise and control groups and grand averaged waveforms from central scouts selected for each group. The maximum activation in the P3m time-window was detected in parietal areas of the cortex. Median amplitude Z-score was 1.78 (1.22–2.41) in the left scout and 1.92 (1.37–6.19) in the right scout for the exercise group and 2.45 (1.28–4.67) in the left scout and 1.33 (0.35–1.82) in the right scout for the control group. Detected sources did not reveal group differences (left scout U[n9,n8] = 43.0, p = .541 and right scout U[n9,n8] = 18.0, p = .093) or significant differences in the activation between hemispheres (exercise group Z = -1.599, p = .110 and control group Z = 0.980, p = .327).

Table 1
Characteristics of the participants presented as mean ± SD or median (IQR). Differences tested with independent samples t-test[a] or Mann-Whitney U test[b].

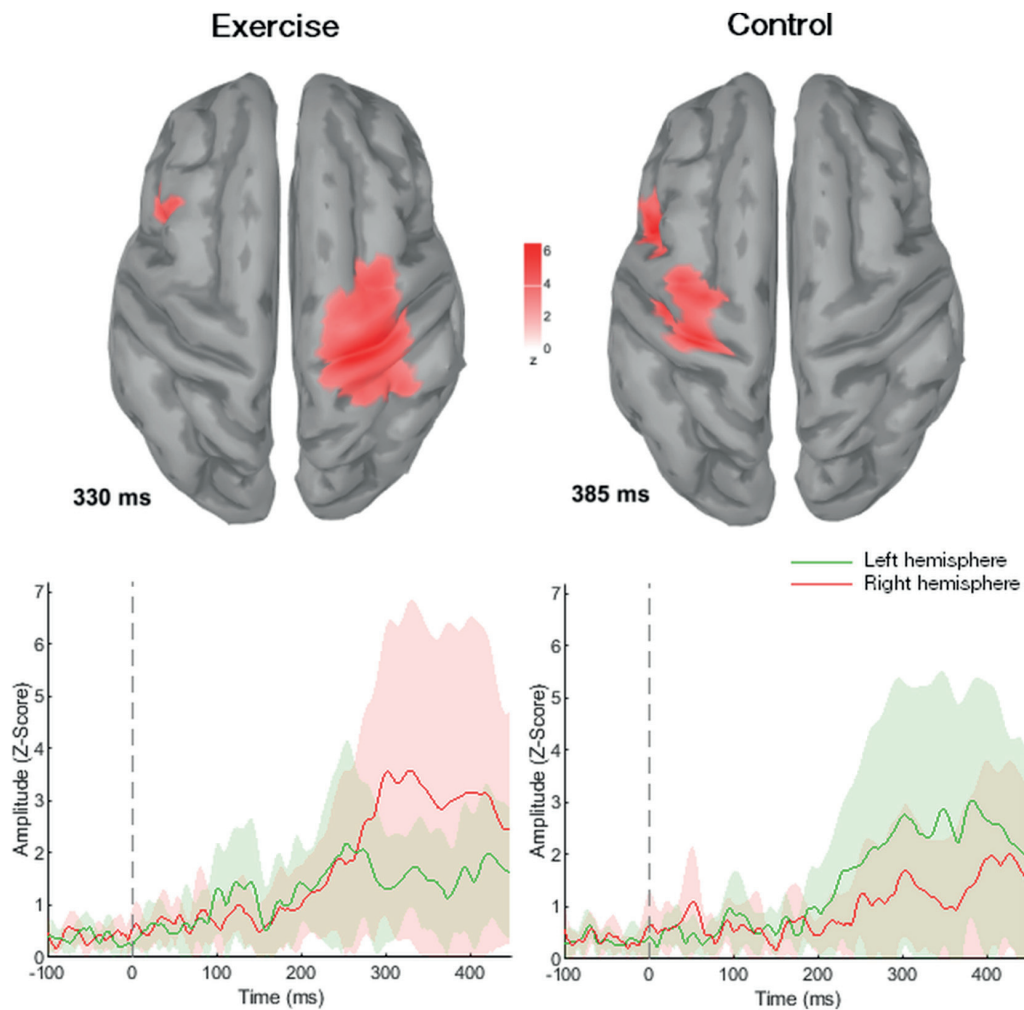|	Exercise (n = 9)	Control (n = 8)	T-value[a]/ U[b]	P-value
Age (y)	77.7 ± 2.1	77.5 ± 2.5	0.150[a]	0.882
Height (cm)	174.0 ± 3.6	173.3 ± 8.4	0.234[a]	0.820
Weight (kg)	80.1 ± 10.6	78.3 ± 8.9	0.366[a]	0.720
Reaction-time (ms)	577 ± 90	528 ± 64	1.292[a]	0.216
Target hit (n)	48.0 (42.0–50.0)	42.5 (35.0–47.5)	19.0[b]	0.114

Fig. 3. Grand average minimum norm estimate -source maps for exercise and control groups at their maximum source amplitudes. Below are scout waveforms created from each group, showing temporal evolution in the central activation sources, separately for both hemispheres.

3.3. Sensor-level analysis

The grand average waveforms obtained from all planar gradiometers are shown in Fig. 2 for the exercise and control groups separately. In single sensor analysis, peak amplitudes were similar in both groups (U [n9,n8] = 30.0, p = .606). Peak amplitude was 89.8 (67.3–98.8) fT/cm in the exercise group and 70.8 (49.4–101.1) fT/cm in the control group. Average amplitudes over the period of 320–390 ms were also similar between groups (59.5 (52.5–76.9) fT/cm for the exercise group and 52.3 (25.3–80.8), U[n9,n8] = 29.0, p = .541) fT/cm for the control group. Peak latency was 352 (346–388) ms in the exercise group and 349 (327–392) ms in the control group (U[n9,n8] = 28.0, p = .481).

3.4. Sensor-group M200 analysis

There were no differences in M200 amplitudes between groups or hemispheres (p = .678 and p = .051, respectively) and groups were similar in hemispheric differences (p = .305). Peak amplitude in exercise group was 40.2 (CI 30.1–50.2) ft/cm in the left temporal region and 37.4 (CI 27.3–47.4) ft/cm in the right temporal region, and in the control group 43.6 (CI 32.9–54.2) in the left temporal region and 34.4 (CI 23.7–45.1) ft/cm in the right temporal region. Latencies were also similar for groups and hemispheres (p = .888 and p = .611 respectively) and groups did not differ in hemispheric differences (p = .299). M200

latency in exercise group was 227.0 (CI 214.0–240.0) ms in left temporal region and 240.4 (CI 227.5–253.4) ms in right temporal region, and in the control group 238.3 (CI 224.5–252.0) ms in the left temporal region and 241.8 (CI 228.0–255.5) ms in the right temporal region.

3.5. Sensor-group P3m analysis

There were no differences in P3m peak amplitudes or average amplitudes between groups in the detected sensor-groups (p = .298, p = .393 and p = .731 for peak amplitudes and p = .219, p = .349 and p = .513 for average amplitudes in frontotemporal, parietal, and temporal sensor-groups, respectively). However, there was a difference in hemispheric activity in peak amplitude and average amplitude in fronto-temporal sensor-groups (p = .043 and p = .008, respectively). The exercise group had stronger P3m peak amplitude and average amplitude in right hemisphere, as the control group in left hemisphere (p = .005 and p = .001 for group*hemisphere effect in peak amplitude and average amplitude, respectively). There was also a significant group difference in hemispheric activity in parietal sensor-groups. The exercise group showed stronger P3m amplitudes in right parietal sensor-group (p = .013 and p = .019 for peak amplitude and average amplitude, respectively). The control group had similar amplitudes in left and right parietal sensor-groups (p = .432 and p = .425 for hemispheric effect in peak amplitude and average amplitude, respectively). Peak amplitudes

and average amplitudes were similar between hemispheres for both groups in temporal sensor-groups ($p = .790$ and $p = .483$ for hemisphere effect and $p = .926$ and $p = .418$ for group*hemisphere effect for peak amplitude and average amplitude, respectively). Because of one outlier in hemispheric difference scores in temporal average amplitudes, a sensitivity analysis was performed without the outlier, showing no difference between groups or hemispheres ($p = .316$ for hemisphere effect and $p = .901$ for group*hemisphere effect). Mean peak and average amplitudes are presented in Table 2.

The control group showed shorter latency in the right temporal sensor-group than the exercise group ($U[n9,n8] = 15.5$, $p = .046$). Peak latency was 360 (335–382) ms for the exercise group and 321 (320–365) ms in the control group. Latency was similar in left temporal sensor group ($U[n9,n8] = 37.5$, $p = .888$) for exercise and control groups (381 (334–387) ms and 363 (335–390) ms, respectively). Latencies were similar in frontotemporal ($U[n9,n8] = 41.0$, $p = .673$ and $U[n9,n8] = 24.0$, $p = .277$ for left and right hemisphere, respectively) and parietal sensor-groups ($U[n9,n8] = 44.0$, $p = .481$ and $U[n9,n8] = 30.0$, $p = .606$ for left and right hemisphere, respectively) between groups. Peak latencies were 341 (322–390) ms and 353 (330–371) ms for the exercise group and 381 (330–389) ms and 326 (321–390) ms for the control group in left and right frontotemporal sensor-groups, respectively. In parietal sensor-groups, peak latencies were 360 (328–387) ms and 344 (326–382) ms in the exercise group and 382 (358–386) ms and 336 (320–386) ms in the control group for left and right, respectively. Grand averaged RSS waveforms for both groups are shown in Fig. 4.

4. Discussion

In our groups of long-term resistance-trained older men and their controls, demographic characteristics were similar, and groups showed no differences in reaction times or their ability to perform target hits. For all participants, averaged deviant epochs revealed bilateral P3m activity in the typical P3 window. In contrast to our hypothesis, we did not find significant differences in P3m amplitudes between groups. However, we found a difference between groups in hemispheric activity of the P3m in frontotemporal and parietal sensor-groups. The exercise group showed stronger activation in the right hemisphere in frontal and parietal regions in a time-window of 320–390 ms compared to the left hemisphere. The control group showed a stronger activation in the left frontotemporal sensor-group compared to the right frontotemporal sensor-group. The control group also showed shorter latency in the right temporal sensor-group than the exercise group.

As topographic maps showed bilateral temporal activation before P3m activity, already in the time window of 200–260 ms, we analyzed M200 activity in temporal sensor-groups. There is evidence that the early detection of deviant somatosensory stimuli is modified by both

aging and exercise background, studied with non-attended somatosensory paradigms (Hautasaari et al., 2017; Strömmer et al., 2014; Strömmer et al., 2017; Tarkka et al., 2016). Our study revealed no differences between the exercise and control groups in M200 amplitudes or latencies. Our stimulus detection task was performed attended with an active oddball paradigm, which is not directly comparable to the previous studies with a non-attended oddball paradigm. No studies to our knowledge have investigated the effects of resistance training on automatic deviant detection, either attended or non-attended.

P3 response is well accepted as a marker of cognitive processing in the brain, and P3 amplitude varies in healthy, experimental, and pathological conditions (Hedges et al., 2016; Polich, 1997; Seer et al., 2016). Aging is one of the major factors affecting P3 amplitude (van Dinteren et al., 2014), and the effects of various forms of physical exercise on P3 during aging have been investigated. Both aerobic exercise and resistance training have enhanced P3 amplitude in intervention studies (Kao et al., 2019; Özkaya et al., 2005; Tsai et al., 2015). Long-term (3-year) aerobic exercise has resulted in larger P3 amplitudes, similarly to years of higher self-reported physical activity background (Kao et al., 2019). However, studies with long-term exercise training are scarce, and the effects of long-term resistance-training have not been investigated previously. Long-term training effects provide beneficial information compared to those achieved in the short-term, as interventions always provide other sudden beneficial attributes as well, such as social activity and learning features, in addition to exercise. Also, self-reported physical activity may contain reporting bias, and a physically active lifestyle may as itself be a result of a better cognitive function in older adults. Our participants were unique in their different exercise backgrounds for ten years, during which time the exercise group had carried out a weekly resistance training schedule. Despite the long-term resistance training background, we did not detect amplitude enhancement in our trained participants. The enhancement of P3 amplitude in shorter intervention studies could have partly resulted from learning features and other novelty factors that do not apply in a long-term follow-up while the training continues. In our groups, there might also be other factors, such as other physical activity habits or education background and leisure-time activities, with cognitive training benefits that we were not aware of, and which may influence the P3m amplitude (Gajewski and Falkenstein, 2018). The large inter-individual variability in P3m amplitudes in the control group could support this explanation, and why we did not detect significant differences.

In our study, we detected bilateral P3m in both groups in accordance with earlier detected somatosensory P3 sources (Tarkka et al., 1996; Valeriani et al., 2001). We observed a difference in the distribution of P3m activity in topographic and source maps and, therefore, also performed a hemispheric analysis. The exercise group showed higher activation in the right parietal and frontotemporal regions, analyzed with sensor-groups, compared to the left parietal and frontotemporal regions. For controls, the left hemisphere had stronger activity in frontotemporal region compared to the right. In somatosensory P3 sources, this type of lateralization has not been reported in earlier studies, to our knowledge (Tarkka et al., 1996; Valeriani et al., 2001). However, Valeriani et al. (2001) reported an additional unilateral frontal source for P3, contralateral to stimulation, with a slightly different dipole modelling technique than in similar studies. In P3 studies with auditory stimulation, pronounced amplitude in the right hemisphere, however, is a more common finding (Gilmore et al., 2009; Frodl et al., 2000). This is theorized to stem from right hemispheric network that is associated with working memory, sustained attention, and target detection. It is possible that in our study, the MEG technique reveals lateralization more sensitively than earlier EEG recordings in the somatosensory domain. It may be hypothesized that our exercise group was able to utilize right hemispheric network in the stimulus detection task more efficiently.

Another explanation for group differences might arise from age-related changes in brain function. Aged individuals are overall reported to use additional brain regions to implement the same cognitive

Table 2
Sensor-group characteristics for P3m peak amplitude and average amplitude (fT/cm) presented as means and 95% confidence intervals (CI), tested with linear mixed model, for group, hemisphere, and group*hemisphere effect.

Sensor-group	Exercise, n = 9 (95% CI)	Control, n = 8 (95% CI)
Peak amplitudes		
Left frontotemporal	35.7 (22.5, 48.9)	50.1 (36.1, 64.1)
Right frontotemporal	48.0 (34.8, 61.2)	38.1 (24.1, 52.1)
Left parietal	38.5 (24.8, 52.2)	48.2 (33.8, 62.9)
Right parietal	52.9 (39.2, 66.6)	44.5 (30.0, 59.0)
Left temporal	46.0 (34.9, 57.0)	43.7 (32.1, 55.5)
Right temporal	47.6 (36.5, 58.6)	44.9 (33.1, 56.6)
Average amplitudes		
Left frontotemporal	25.1 (13.3, 36.8)	43.2 (30.9, 55.7)
Right frontotemporal	38.2 (26.5, 49.9)	27.8 (15.4, 40.2)
Left parietal	27.8 (15.1, 40.4)	38.6 (25.1, 52.0)
Right parietal	42.7 (30.0, 55.3)	34.1 (20.7, 47.6)
Left temporal	36.2 (25.8, 46.6)	35.5 (24.5, 46.6)
Right temporal	37.8 (27.4, 48.2)	32.9 (22.9, 44.0)
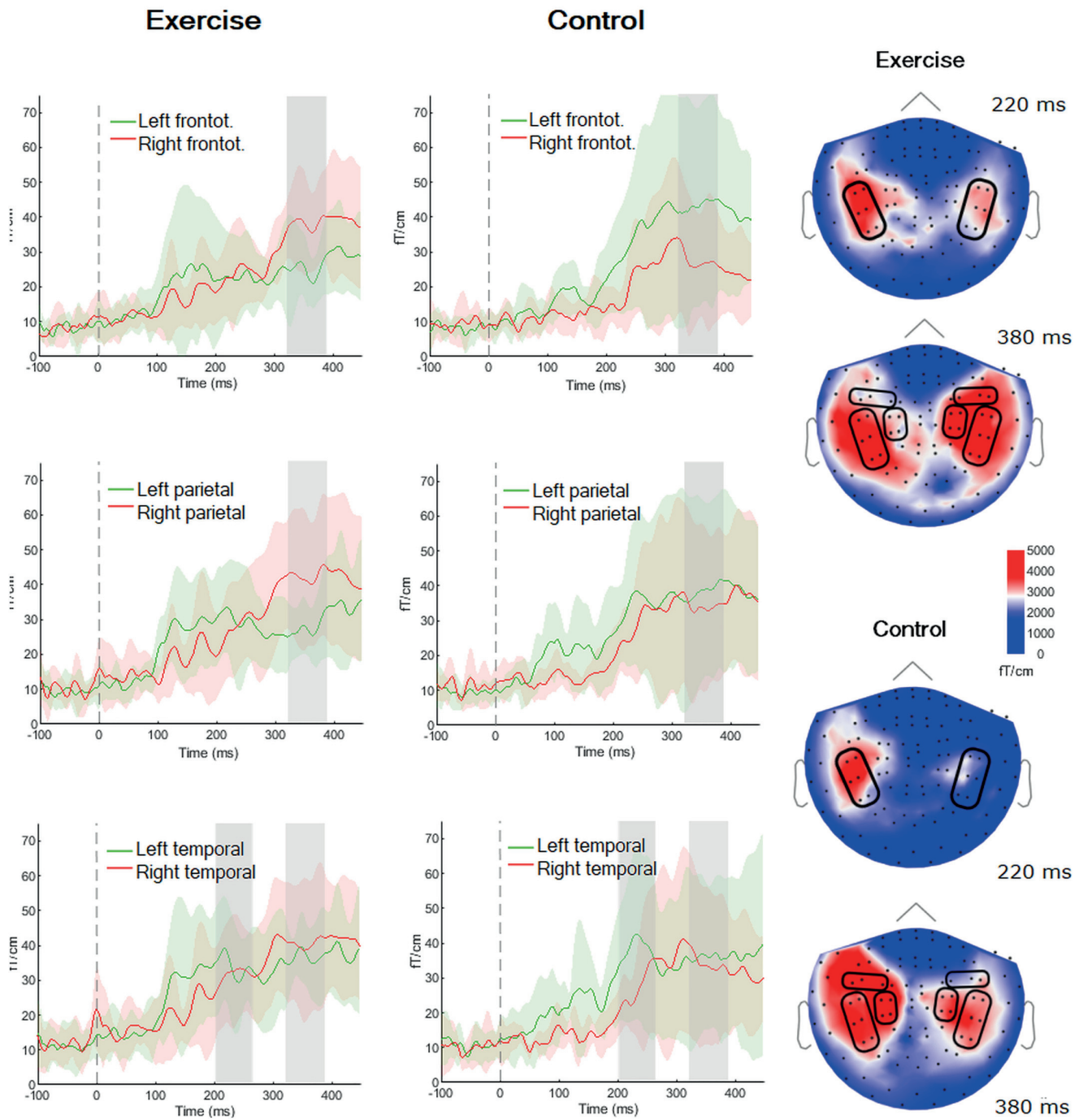
Fig. 4. Grand average waveforms (±SD) in frontotemporal, parietal, and temporal sensor-groups for exercise and control groups, both hemispheres are shown in each graph. Grey shaded area demonstrates the analyzed time window in each sensor-group. Topographic maps show grand averages of both groups in planar gradiometer activity at 220 and 380 ms after stimulus onset. Black squares indicate the sensor-groups selected for analysis.

tasks as young (Reuter-Lorenz and Park, 2010). Regarding the P3 component, a typical observation to occur during aging is frontal compensation (van Dinteren et al., 2018). P3 is considered to arise from many independent sources and their complex connections. In P3 generation, hemispheres may also have individual roles, as hemispheric specialization is a well-known principle in both sensory and cognitive processing (Banich, 2009; Tang et al., 2017). Cabeza (2002) have introduced a theoretic model called "hemispheric asymmetry reduction in older adults" (HAROLD) as a part of the compensatory mechanism theory occurring in the aging brain. The model arises from the evidence

that different cognitive functions seem to be less lateralized in older adults than in young adults. That has been suggested to reflect compensatory processes and dedifferentiation processes, which refer to the regional loss of specialization in the brain. Our results indicate lateralization in both groups in generation of somatosensory P3m. Our exercise group seemed to be able to activate the right hemisphere, ipsilateral to stimulation, more effectively than the left hemisphere, and the controls had stronger activity on the left hemisphere. With our participants, it is unclear whether the lateralization is associated with better or poorer performance, as we did not detect significant differences

in reaction times and target hits. We do not have information on our participants' cognitive performance; thus, we cannot discuss whether the asymmetry is associated with high cognitive function. Without detailed information of our participants' cognitive status, the origins for the detected differences in brain function are not entirely clear. However, our results might suggest stronger right hemisphere activation arising from working memory and attentional processes (Gilmore et al., 2009). Both of our groups of aged individuals may utilize compensatory brain mechanisms for the deviant detection task, but perhaps there are differences in this development. Further studies with young and old individuals would be necessary to further confirm this.

In P3m latency analysis with sensor-groups, the control group revealed shorter latencies in the right temporal region than the exercise group. Shorter P3 latencies are found to increases with age in late adulthood and correlate with better cognitive performance (Pelosi et al., 1992; van Dinteren et al., 2014). In young individuals, physical activity has resulted in shorter P3 latency, but in the aging population, the results vary considerably (Kao et al., 2019). No studies have found a connection between resistance training and P3 latency modulation in aging individuals. Shorter latency may indicate faster processing of the target stimulus in the control group. However, in our sensor-group RSS values, the peak of the waveform may not properly describe the real latency of the P3 as there are multiple sensors and processes that affect the amplitude peak of the wave. Therefore, the peak value may not represent the real latency of the P3m phenomenon. Furthermore, the difference in P3m latency was not visible in other regions with stronger P3m amplitude and therefore we cannot make strong conclusion of this difference.

The major strength of our study is the unique study design of an exercise group with a long-term, ten-year resistance training background and the otherwise very similar non-training control group.

5. Limitations

Our study has some limitations. Our participants were part of a larger, ten-year project where various exclusion criteria were applied, and thus our final sample size was rather small. Our MEG measurements were a later addition to the on-going project, which is the reason that we have no data recorded at the start of the intervention period. Furthermore, we were not able to perform formal cognitive testing, however, the present participants were free of neurological or musculoskeletal diseases (see Methods). Four participants in the control group were new recruits, and therefore were not part of the original randomization. Also, they did not take part in the measurements at the beginning and during follow-up of the original study. This study was not an intention-to-treat trial and participants who developed neurological or psychiatric diseases were excluded from MEG recordings. Therefore, we cannot draw conclusions on possible effect of resistance training on brain pathologies and their development. Our results present an opening in the field and further research with complete cognitive testing and structural brain imaging would be necessary to fully understand the relationship between resistance training and cognitive aging.

6. Conclusions

Ten-year resistance training background in older men did not lead to significant differences in P3m amplitude over their nonresistance-trained controls. However, we found stronger right hemisphere contributions in P3m generation in resistance-trained individuals and stronger left hemisphere contribution in their untrained controls. This finding suggests not entirely symmetrical P3m activation in the aging brain and possibly modulation in the age-related compensatory mechanisms in the P3m generation due to long-term resistance training background.

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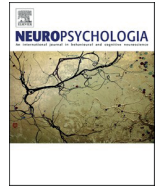
III

MAGNETOENCEPHALOGRAPHY REVEALS IMPAIRED SENSORY GATING AND CHANGE DETECTION IN OLDER ADULTS IN THE SOMATOSENSORY SYSTEM

Pesonen, H., Strömmer, J., Li, X., Parkkari, J., Tarkka, I. M. & Astikainen, P. 2023

Magnetoencephalography reveals impaired sensory gating and change detection in older adults in the somatosensory system

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ABSTRACT

Brain electrophysiological responses can provide information about age-related decline in sensory-cognitive functions with high temporal accuracy. Studies have revealed impairments in early sensory gating and pre-attentive change detection mechanisms in older adults, but no magnetoencephalographic (MEG) studies have been undertaken into both non-attentive and attentive somatosensory functions and their relationship to ageing. Magnetoencephalography was utilized to record cortical somatosensory brain responses in young (20–28 yrs), middle-aged (46–56 yrs), and older adults (64–78 yrs) under active and passive somatosensory oddball conditions. A repeated standard stimulus was occasionally replaced by a deviant stimulus ($p = .1$), which was an electrical pulse on a different finger. We examined the amplitudes of M50 and M100 responses reflecting sensory gating, and later components reflecting change detection and attention shifting (M190 and M250 for the passive condition, and M200 and M350 for the active condition, respectively). Spatiotemporal cluster-based permutation tests revealed that older adults had significantly larger M100 component amplitudes than young adults for task-irrelevant stimuli in both passive and active condition. Older adults also showed a reduced M250 component and an altered M350 in response to deviant stimuli. The responses of middle-aged adults did not differ from those of younger adults, but this study should be repeated with a larger sample size. By demonstrating changes in both somatosensory gating and attentional shifting mechanisms, our findings extend previous research on the effects of ageing on pre-attentive and attentive brain functions.

1. Introduction

Healthy ageing is associated with various degrees of decline in sensory-cognitive functions, such as attention, working memory, and executive function (Hedden and Gabrieli, 2004). Changes in cognitive performance result from changes in both brain structure and function (Harada et al., 2013; Reuter-Lorenz and Park, 2010).

Electroencephalography (EEG) and magnetoencephalography (MEG) recordings of brain activity provide a useful tool for investigating age-related changes in the sensory-cognitive functions of the brain due to their high temporal resolution. Studies of early automatic sensory processing have demonstrated a decrease in sensory inhibition – that is, sensory gating – in ageing adults (Alain et al., 2022; Bolton and Staines, 2012; Friedman, 2012; Terrasa et al., 2018). Sensory gating is a mechanism that supports adaptive behaviour by inhibiting neural responses to repetitive events, which are irrelevant to the task at hand (Boutros

and Belger, 1999; Jones et al., 2016). This reduced inhibition in older adults is thought to hinder the ability to focus attention on information relevant to the task at hand (Bolton and Staines, 2012; Gazzaley et al., 2005; Reuter-Lorenz and Park, 2010; Yang et al., 2019). Age-related changes in sensory gating have been observed as increased amplitudes of the early sensory event-related potentials (ERPs) in older compared to younger individuals in different sensory modalities (Alain et al., 2022; Bolton and Staines, 2012; Cheng et al., 2015; Terrasa et al., 2018; Yang et al., 2019). Somatosensory oddball paradigms, in which a repetitive 'standard' stimulus is occasionally replaced by a rare 'deviant' stimulus, have revealed larger P50 and N80 (Strömmer et al., 2017) and P100 (Bolton and Staines, 2012) amplitudes in older adults than younger adults.

Later evoked responses that are also commonly associated with age-related decline are mismatch negativity (MMN or mismatch response [MMR], due to its positive polarity in the somatosensory ERPs) and P3,

which are more closely related to cognitive processing of sensory input (Friedman, 2003; Kamp, 2020; Näätänen et al., 2012; Polich, 1996; Ruzzoli et al., 2012). Mismatch negativity was first identified in the auditory modality (Näätänen et al., 1978) and is thought to reflect a prediction error in the brain's hierarchical sensory processing (Friston, 2005). According to predictive coding theory, the brain forms predictions about the sensory environment based on prior sensory inputs (Friston, 2005; Garrido et al., 2009). Prediction errors are then projected to higher levels of hierarchical networks to further update predictions (Friston, 2005).

Mismatch negativity is traditionally elicited in a passive oddball paradigm, where it is observed approximately 150 ms–250 ms after the onset of the deviant stimulus. In addition to the auditory modality, MMN has been confirmed in the visual, somatosensory, and olfactory modalities (Astikainen et al., 2008; Czigler and Kojouharova, 2022; Hautasaari et al., 2018; Krauel et al., 1999; Kreegipuu et al., 2013; Stefanics et al., 2012; Strömmer et al., 2014; Xu et al., 2021). Somatosensory MMR (sMMR) has been found in both EEG (Akatsuka et al., 2005; Kangas et al., 2021; Kekoni et al., 1997; Spackman et al., 2010; Strömmer et al., 2017) and MEG studies (Akatsuka et al., 2007; Hautasaari et al., 2017, 2018; Naeije et al., 2016, 2018; Xu et al., 2021) for changes in stimulus location, intensity, duration and vibratory frequency, for example. Although sMMR has been significantly less studied in the older adult population than its auditory counterpart, there is evidence of sMMR deterioration in older adults (Strömmer et al., 2014, 2017).

Studies using active somatosensory oddball paradigms have reported an N250 component corresponding to the N200 in the auditory modality. This component reflects attentional and behavioural processes during oddball discrimination tasks (Huang et al., 2005; Kekoni et al., 1996; Kida et al., 2003). However, there is no evidence of age-related deterioration in this component.

The P3 component is known to index sensory-cognitive processes involved in the evaluation and categorization of distractor stimuli (Polich, 2007). In the literature, P3 is further divided into two distinct components, P3a and P3b. The P3a component is elicited either when the stimulus is novel or when the deviant stimulus is intentionally ignored. It is thought to represent stimulus evaluation processes and the orientation of attentional resources (Friedman et al., 2001). P3b, elicited in tasks requiring sustained attention to rare target stimuli, is associated with the updating of working memory (Polich, 2007; Polich and Criado, 2006). Measures of P3b are closely linked to performance on cognitive tests (Walhovd and Fjell, 2003). Furthermore, P3b has been clearly shown to deteriorate with ageing, demonstrating a more frontal cortical distribution in older than in younger adults (Dinteren et al., 2018; Polich, 1997; Reuter et al., 2017). Signs of this have already been seen in middle-aged adults, and in the somatosensory modality, late middle-aged adults (55–65 y) have shown a frontal shift in P3b activity (Dinteren et al., 2014a; Reuter et al., 2013).

The aim of the present study was to investigate whether cortical sensory-cognitive functions are modulated in middle-aged and older adults compared to young adults, as reflected in MEG responses. Previous studies have not used MEG to investigate predictive sensory processing in older adults, and since no ageing studies have used passive and active paradigms for the same participants, we applied both conditions. We also performed cognitive tests on all participants to assess group characteristics in cognitive abilities. We hypothesized that early sensory responses elicited before 100 ms after stimulus onset would be enlarged in older compared to younger adults, thus reflecting impaired sensory gating in older adults. By contrast, MMR and P3 – reflecting change detection and attentional shifts to deviant stimuli, respectively – are expected to be reduced in amplitude in older adults. Somatosensory MMR has shown reduced amplitudes in older adults in our previous ERP studies (Strömmer et al., 2014, 2017), but MEG results are lacking. In a previous ERP study, the parietal P3b in particular showed decreased amplitudes in older adults, while no difference was found between older and younger adults in the frontal P3a (Dinteren et al., 2018). In our

previous ERP study, we did not observe amplitude differences in somatosensory or auditory P3a in a passive oddball condition between older and younger adults (Strömmer et al., 2017). Therefore, it is possible that the differences are found only in the P3b elicited in the active oddball condition and not in the P3a elicited in the passive oddball condition. We also hypothesized that middle-aged adults might show changes in sensory-cognitive processing, as reflected by attenuated amplitudes of the later cognitive components (Dinteren et al., 2014a; Reuter et al., 2013).

2. Materials and methods

2.1. Participants

The sample size was estimated based on previous studies using similar somatosensory stimulation and paradigms similar to the present study in young (Xu et al., 2021) and older adults (Strömmer et al., 2014). Initially, 22 young, 11 middle-aged and 15 older adults volunteered for MEG measurements during the data collection period of the study, but data from some participants were excluded due to technical difficulties during recording (n = 5) or lack of obligatory components in the MEG signal (n = 6). Therefore, the final sample consisted of 15 young adults (age between 20 and 28), 7 middle-aged adults (age between 46 and 56) and 15 older adults (age between 64 and 78).

Participants were recruited through email lists at the University of Jyväskylä and the University of the Third Age (an open university in Jyväskylä aimed at older adults interested in science). Inclusion criteria were female gender, right-handedness, good general health, and age of either 18–30, 45–60, or 64–80 years. Female gender was chosen because of the difficulty in recruiting male volunteers and the goal of making the groups comparable. Exclusion criteria were pregnancy or lactation, diagnosed neurological or psychiatric disease, medication affecting the central nervous system, previous brain surgery, drug or alcohol addiction, any sensory deficits (except vision corrected with glasses), speech disorders, dyslexia or attention deficit disorder, acute life crisis or stressful life situation, and any metallic implants or braces preventing participation in MEG recordings. All participants completed a questionnaire on their health status, education, and physical activity habits (hours/week, months/year), as well as the Beck Depression Inventory-II (BDI-II). A mini-mental state examination (MMSE) was administered to older adults. The study was approved by the Ethical Committee of the Central Finland Health Care District and the study was conducted according to the guidelines of the Declaration of Helsinki. All participants signed an informed consent and were aware of their right to withdraw at any time. Information on the participants is presented in Table 1.

2.2. Cognitive tests

Cognitive abilities were assessed using a neuropsychological test battery consisting of the following eight tests: the Rey Auditory Verbal Learning Test (RAVLT; Lezak, 1995), the Rey-Osterrieth Complex Figure Test (ROCF; Brauer Boone, 2000), the Logical Memory Task (Lezak, 1995), the Trail Making Test A and B (TMT-A; TMT-B; Bowie and Harvey, 2006), the Stroop Color-Word Test (Alvarez and Emory, 2006), the Digit Span Task (Ramsay and Reynolds, 1995) both forwards and backwards, the Letter-Number Sequencing task (LNS; Crowe, 2000) and the Verbal Fluency Test, a version of the Controlled Oral Word Association (Lezak, 1995). Motor skills were also tested with the Finger Tapping task (Ruff and Parker, 1993), and the Handgrip Test. The test battery was administered in the same order to all participants and was scheduled within approximately one week of participation in the MEG measurements. The tests were administered by a psychologist, or a trained psychology student, and the duration of the entire test battery was approximately 1–1.5 h per participant.

Table 1

Characteristics of the participants. Values are presented as means and standard deviations (Mean ± SD) or number (n) and percentage of the number of participants in the group (%).

	Young adults (n = 15)	Middle-aged adults (n = 7)	Older adults (n = 15)
Age (year)	23.4 ± 2.2	52.4 ± 3.5	69.1 ± 4.2 †
Height (cm)	164.7 ± 4.3 †	168.1 ± 4.8	161.5 ± 5.4 (n = 11)
Weight (kg)	61.0 ± 7.3 (n = 13)	75.1 ± 18.1	62.2 ± 8.5 (n = 10)
Education (n (%))	†		†
Upper secondary	9 (64)	3 (43)	8 (57)
Bachelor's degree	1 (7)	0	0
Graduate degree	4 (29)	4 (57)	6 (43)
BDI-II	1.5 ± 1.5	5.3 ± 6.1	4.6 ± 4.1 †
MMSE			28.3 ± 1.2 (n = 13)
PA hour/week (n (%))	†		†
0-2	4 (28.5)	3 (43)	4 (29)
2-4	6 (43)	3 (43)	4 (29)
over 4	4 (28.5)	1 (14)	6 (43)

† = missing information from one participant. BDI-II = Beck's Depression Inventory-II, MMSE = Mini-Mental State Examination; PA = Physical activity.

2.3. Stimuli and task

Somatosensory oddball stimulation conditions were performed, in which electrical pulses of 200 μs duration were delivered to the participant's *left* index and little fingers, with a 500 ms stimulus-onset asynchrony. For both fingers, two non-magnetic ring electrodes were placed above the proximal and distal phalanges, stimulating the cathode and anode, respectively. In the oddball condition, a repeated standard stimulus was rarely replaced by a deviant stimulus (p = .1) delivered to a different finger than the standard stimulus (location deviant). Stimuli were presented in a pseudorandom order, with at least two standard stimuli delivered between consecutive deviant stimuli. The assignment of the two finger locations as standard and deviant was counterbalanced between two blocks of stimuli. The stimulus intensity was set to 150% of the individual sensory threshold, which was tested separately for each finger before the experiment. Mean stimulus intensities were 2.3 ± 0.6 mA and 2.0 ± 0.6 mA for young adults, 3.1 ± 0.8 mA 2.6 ± 0.3 mA for middle-aged adults, and 3.9 ± 1.4 mA and 3.2 ± 0.8 mA for older adults for the index and little fingers, respectively. Stimulus intensities for both fingers were significantly higher for older adults than for young adults (index finger: p < .001, mean difference 1.6 mA, and little finger: p < .001, mean difference 1.1 mA), which is a common finding for electrical thresholds in older adults (Kemp et al., 2014). The experiment was conducted in two different conditions. In a *passive*, non-attended condition, participants were instructed to ignore any stimuli and focus on a silent movie on a screen placed approximately 1.5 m in front of them. In an *active*, attended condition, participants were instructed to focus on the stimuli and to press a button with their *right* index finger as soon as they detected a deviant stimulus. In the active condition, participants were instructed to keep their eyes fixed on a cross in the centre of the screen. There were 1000 stimuli in each condition, which were presented in two blocks. In one block, the deviant stimulus was delivered to the index finger and the standard stimulus to the little finger. In the second block, this assignment was reversed. Stimulus presentation was controlled by the Presentation software (Neurobehavioral Systems, Inc., Albany, CA, United States).

### 2.4. Collection of magnetoencephalographic data

Somatosensory evoked field recordings were conducted with a 306-sensor MEG device (Elekta Neuromag®, Triux™, Stockholm, Sweden) in a magnetically shielded room with a bandpass of 0.1–330 Hz and a sampling rate of 1000 Hz. Eye blinks and movements were recorded with an electro-oculogram (EOG), with electrodes placed above and below the right eye (the vertical EOG) and on the outer canthi of both eyes (the horizontal EOG). Heartbeats were recorded with an electro-cardiogram (ECG) with two electrodes placed on the chest. Five head position indicator (HPI) coils were placed on the scalp to register the participant's position relative to the MEG sensors in the helmet: three on the forehead and two behind the ears. The position of the coils was registered with a 3D digitizer (Fastrak®, Polhemus, Vermont, USA) in addition to the nasion and preauricular points and over 100 head shape indicators around the scalp. During recording, the MEG was set in a 68° upright gantry position, and participants were instructed to sit comfortably and still, with their hands resting on the table and on the response box (when in use), and to avoid extensive blinking and muscle tension. All data were stored for offline analysis.

2.5. Data analysis

Temporal signal space separation (tSSS; Taulu and Simola, 2006) in Maxfilter software (Elekta Neuromag®, Stockholm, Sweden) was utilized to reduce external artifacts and to detect unacceptable MEG channels. Data preprocessing was initially conducted using Brainstorm software (Tadel et al., 2011). The data were bandpass filtered at 1–40 Hz. Eye blink and heartbeat artifacts were detected and removed using signal-space projection (SSP; Uusitalo and Ilmoniemi, 1997). Data were segmented into epochs −100 ms before and 500 ms after stimulus onset. Epochs with EOG traces exceeding 200 μV or amplitudes larger than 3000e-13 T/m for gradiometers and 4e-12 T for magnetometers were removed. The remaining epochs were also visually inspected, and epoch processing was continued in MNE python (Gramfort et al., 2014). Data from participants with no visible obligatory components were excluded from further analysis. For the *passive* condition, the number of participants finally accepted for each group was 12 young, 7 middle-aged, and 14 older adults. For the *active* condition, the final accepted number of participants for each group was 12 young, 6 middle-aged, and 12 older adults. Deviant epochs for both stimulation blocks and an equivalent number of standard epochs preceding a deviant in each block were averaged separately for each subject. The minimum number of accepted trials was 48 out of 100 per condition.

After individual averaging, grand averages were calculated for each age group and condition. The grand average waveforms of the somatosensory evoked field (SEF) responses (Fig. 1), together with previous literature (Dinteren et al., 2014b; Strömmer et al., 2014; Tarkka et al., 1996; Terrasa et al., 2018) were used to define the time windows for the statistical analyses. For both *passive* and *active* conditions, M50 and M100 peaks were identified for early components, and time windows of 30 ms–80 ms and 81 ms–120 ms, respectively, were used to analyse standard and deviant stimuli separately. In the *passive* condition, late somatosensory responses were analysed in two time windows: M190 between 121 ms and 220 ms, and M250 between 221 ms and 290 ms post-stimulus latency. In the *active* condition, M200 between 120 ms and 270 ms, and M350 between 271 ms and 380 ms post-stimulus latency were investigated. Time windows for later components were defined based on grand average waveforms (Fig. 1) and previous literature on somatosensory oddball responses – with M190 and M250 corresponding to MMR and P3a for the *passive* condition and M200 and M350 corresponding for N250 and P3b for the *active* condition (Hautasaari et al., 2017, 2018; Kangas et al., 2021; Kekoni et al., 1997; Kida et al., 2003; Naeije et al., 2018; Strömmer et al., 2014, 2017; Tarkka et al., 1996). Later components (M190 and M250 for the *passive* condition and M200 and M350 for the *active* condition) were analysed for deviant stimuli, as they were detected specifically for the deviants in the grand average waveforms. Fig. 1 presents grand average waveforms for gradiometer pairs (root mean square, RMS) selected according to topographic maps for each time window in passive and active conditions for each group.
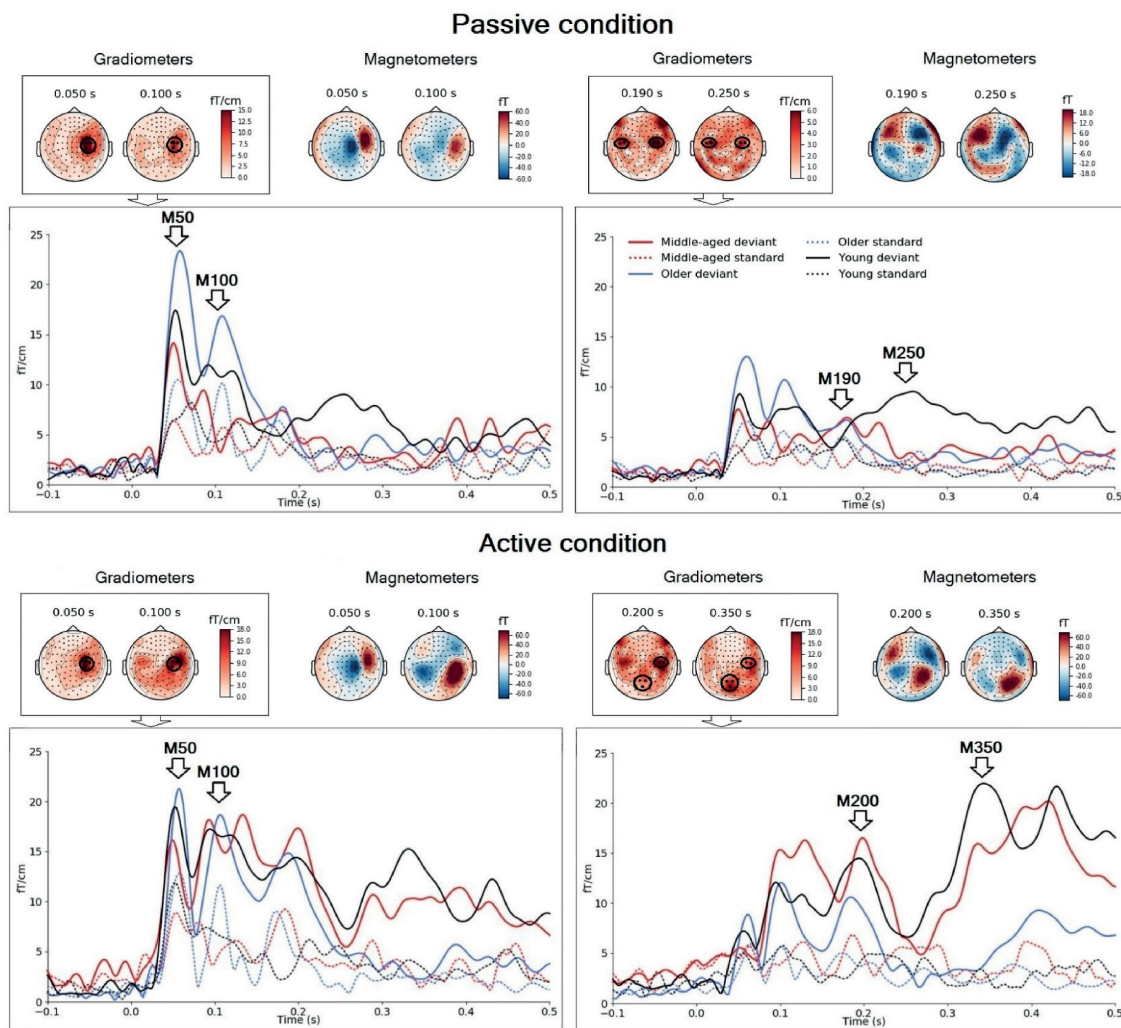
Fig. 1. Descriptive illustration of the evoked responses in the passive (above) and active (below) conditions. The grand average waveforms of selected gradiometer sensor pairs (see Methods) for both deviant (solid line) and standard (dashed line) stimuli (below), and the grand average topographic maps for all participants (n = 33 for passive and n = 30 for active condition) for gradiometers (RMS) and magnetometers separately. The gradiometer pairs selected for the analysis are highlighted and circled. Analysed components are indicated by arrows and acronyms in the waveforms.

2.6. Analysis and statistical tests for behavioural responses and cognitive tests

The average reaction time and the number of correctly identified deviant button presses during the active oddball condition were calculated for each participant. Only responses to correctly identified deviant stimuli within 1100 ms of deviant stimulus onset were included in the analysis. Statistical testing for behavioural responses during the active condition and cognitive test scores were performed using IBM SPSS Statistics for Windows (Version 26.0. Armonk, NY: IBM Corp). Differences between groups were tested with one-way ANOVA. Post hoc tests with Bonferroni correction were applied to investigate significant ANOVA results. The alpha level for significant difference was set at <0.05.

2.7. Statistical tests for brain activity

We used spatiotemporal cluster-based permutation test in MNE Python (Gramfort et al., 2013) to compare whole-head spatiotemporal activity based on a two-sample independent *t*-test. We used the group of young adults as a reference group to compare the responses of middle-aged adults and older adults separately. This analysis was performed instead of a one-way ANOVA due to the small number of participants in the middle-aged group. Each component was analysed separately in the selected time windows. The number of permutations was set to 1,000, and the threshold was set to the equivalent of an F-value of 7 for more localised effects. The alpha level for significant clusters was set at <0.05. Magnetometers and gradiometers were analysed separately, as magnetometers demonstrated qualitatively different activity (see Fig. 5). In addition, we were able to compare the M100 component between the active and passive conditions separately within the groups of young adults and older adults, as this response had a similar latency for both conditions. Conditions were compared using a spatiotemporal cluster-based permutation test based on a pairwise *t*-test. The number of permutations was set to 1,000, and the threshold was set to the equivalent of a t-value of 3 for more localised effects. Magnetometers and gradiometers were analysed separately, and the alpha level for significant clusters was set at <0.05.

3. Results

3.1. Cognitive tests

The results of the cognitive and motor ability tests are presented in Table 2. In all participant groups, the test scores were approximately average or 1 SD above the mean compared to the normative samples (Kivisaari et al., 2009; Mathiowetz et al., 1985; Reinvall and Poutiainen, 2008; Wechsler, 2012). Within our sample, young adults performed better than older adults on cognitive tests in several modalities, including memory (RAVLT, ROCF-test, logical memory delayed, digit-span backwards, LNS), processing speed (TMT-A), and executive function (TMT-B, Stroop 1, verbal fluency). Young adults also performed better on tapping speed and had higher handgrip strength than older adults, indicating better motor skills. Middle-aged adults performed better than older adults on some measures of memory, processing speed and executive function (ROCF-test, TMT-A and -B, Stroop 1, LNS, and tapping speed). No differences were found between young and middle-aged adults.

3.2. Passive condition

M50 and M100 were tested for group differences in the passive condition in the latency range of 20 ms–80 ms and 81 ms–120 ms, respectively, separately for standard and deviant stimulus responses. No group differences were found for M50. The spatiotemporal permutation test for gradiometer data revealed a significant difference between young and older adults in M100 for deviant stimuli in the 82 ms–116 ms time window and for standard stimuli in the 92 ms–120 ms time window (p = .005 and p = .044, respectively). The M100 component was larger for older adults than young adults (Fig. 2). No differences were found between the young and middle-aged groups.

The later components, M190 and M250, were tested for deviant stimulus responses in the latency range of 121 ms–220 ms and 221 ms–290 ms, respectively. No differences were found for the M190 response. The spatiotemporal permutation test for gradiometer data revealed a difference between young and older adults in the M250 component in the time window of 238 ms–286 ms (p = .046). The M250 component was larger in contralateral parietal areas for young adults than older adults (Fig. 3). No differences were found between the young and middle-aged groups.

3.3. Active condition

The average number of targets recognized out of 100 was 84.0 (±9.4) for young adults, 85.5 (±12.9) for middle-aged adults, and 84.7 (±14.7) for older adults. There were no differences between groups in target recognition (F[2,27] = 0.030, p = .971). Reaction times to targets were also similar between groups; 0.440 ± 0.052 for young adults, 0.454 (±0.058) for middle-aged adults, and 0.504 (±0.112) for older adults (F [2,27] = 1.967, p = .159).

M50 and M100 in the active condition were tested in the latency range of 20 ms–80 ms and 81 ms–120 ms, respectively, for standard and deviant separately. No differences were found for M50. The spatiotemporal permutation test for gradiometer data revealed a significant difference between young and older adults in the M100 for the standard stimulus in the 100 ms–120 ms time window (p = .008). Larger standard M100 activity was found in older adults than young adults (Fig. 4). No differences were found between the young and middle-aged groups.

The later components M200 and M350 were tested in the time windows of 120 ms–250 ms and 251 ms–380 ms, respectively. No differences were found between groups for the M200 response. The spatiotemporal permutation test revealed a difference between young and older adults for one cluster in gradiometers in the 252 ms–354 ms time window (p = .044) and two clusters in magnetometers in the 252 ms–380 ms (p = .021) and 286 ms–378 ms (p = .025) time windows for the M350 response. The significant cluster in gradiometers indicated a more pronounced fronto-central activity in older adults than young adults. The orientation of magnetometer waveforms and topographic maps indicated an activity on the fronto-central sensors in older adults, whereas activity in this latency range was more parietally and occipitally pronounced in young adults (Fig. 5). No differences were found

Table 2

Cognitive and performance test scores for each group presented as means and standard deviations (Mean ± SD). Differences between groups tested with one-way ANOVA, and the following post hoc tests with the Bonferroni correction. Statistically significant differences flagged.

	Young adults	Middle-aged adults	Older adults	F-value (df)	P-value	Bonferroni post hoc	η_p^2
RAVLT 1 (points)	8.7 ± 1.9	6.7 ± 1.3	6.4 ± 1.9	6.471 (2,32)	.004**	y-o**	.288
RAVLT 5 (points)	14.4 ± 0.6	13.6 ± 1.3	12.6 ± 1.7	6.823 (2,32)	.003**	y-o**	.299
RAVLT B-list (points)	8.1 ± 2.9	8.5 ± 2.9	5.7 ± 1.8	5.951 (2,28)	.007**	y-o*	.298
RAVLT delay 1 (points)	14.1 ± 0.9	12.1 ± 2.1	9.7 ± 3.4	11.183 (2,32)	<.001***	y-o***	.411
RAVLT delay 2 (points)	13.9 ± 1.0	12.1 ± 2.7	9.4 ± 3.2	11.836 (2,32)	<.001***	y-o***	.425
ROCF copy (points)	35.6 ± 0.9	35.3 ± 1.5	31.3 ± 5.9	4.991 (2,32)	.013*	y-o*	.238
ROCF 2 min (points)	25.8 ± 6.7	24.3 ± 4.7	14.3 ± 6.7	12.777 (2,32)	<.001***	y-o***, m-o**	.444
ROCF 1 h (points)	25.7 ± 5.7	24.3 ± 4.2	13.5 ± 6.4	17.592 (2,32)	<.001***	y-o***, m-o***	.524
Logical memory (points)	28.9 ± 5.8	25.8 ± 8.8	22.4 ± 8.2	2.656 (2,32)	.073		.142
Logical memory delayed (points)	27.5 ± 6.9	22.8 ± 9.3	19.4 ± 8.6	3.396 (2,30)	.047*	y-o*	.185
TMT-A (s)	28.0 ± 8.1	32.1 ± 7.6	50.3 ± 18.4	10.676 (2,32)	<.001***	y-o ***, m-o*	.400
TMT-B (s)	64.4 ± 23.8	69.7 ± 19.3	126.1 ± 58.8	8.868 (2,32)	<.001**	y-o ***, m-o*	.357
Stroop 1 (s)	49.0 ± 7.4	44.9 ± 6.3	56.9 ± 9.0	6.446 (2,32)	.004**	y-o*, m-o**	.287
Stroop 2 (s)	71.4 ± 20.5	60.6 ± 12.5	74.4 ± 9.0	1.975 (2,32)	.152		.110
Stroop 3 (s)	106.8 ± 20.2	107.4 ± 19.8	130.2 ± 31.1	3.588 (2,32)	.039*	(y-o p = .057)	.183
Digit span (points)	9.4 ± 1.2	9.0 ± 1.4	8.5 ± 1.8	1.290 (2,32)	.289		.076
Digit span backwards (points)	7.5 ± 1.3	7.4 ± 0.8	6.1 ± 1.7	3.928 (2,32)	.030*	y-o*	.197
LNS (points)	11.4 ± 2.2	12.2 ± 1.5	8.1 ± 2.4	11.195 (2,31)	<.001***	y-o***, m-o**	.419
LNS max span	5.9 ± 2.5	5.5 ± 0.8	4.5 ± 1.3	2.110 (2,31)	.138		.120
Verbal fluency "k" (word/60s)	25.3 ± 4.1	22.8 ± 6.2	20.6 ± 7.3	2.203 (2,31)	.128		.124
Verbal fluency "s" (word/60s)	19.3 ± 5.4	19.8 ± 4.8	19.0 ± 7.1	0.039 (2,31)	.962		.002
Verbal fluency animal (word/60s)	29.5 ± 6.4	35.5 ± 7.8	24.4 ± 7.4	5.427 (2,31)	.010*	m-o**	.259
Tapping left (taps/10 s)	47.8 ± 5.0	48.1 ± 4.8	39.3 ± 4.9	12.842 (2,31)	<.001***	y-o***, m-o***	.453
Tapping right (taps/10 s)	55.1 ± 4.9	53.0 ± 5.7	41.3 ± 2.2	38.071 (2,31)	<.001***	y-o***, m-o***	.711
Handgrip left (kg)	29.2 ± 5.1	27.3 ± 9.1	20.4 ± 5.7	6.723 (2,30)	.004**	y-o**	.309
Handgrip right (kg)	28.9 ± 5.3	27.0 ± 9.8	22.0 ± 5.1	3.867 (2,30)	.032*	y-o*	.205

* = p < .05, ** = p < .01, *** = p < .001, η_p^2 = partial eta squared, df = degrees of freedom, y = young adults, m = middle aged adults, o = old adults, RAVLT = Rey Auditory Verbal Learning Test, ROCF = Rey-Osterreich Complex Figure Test, TMT = Trail Making Test, LNS = The letter-number sequencing task.
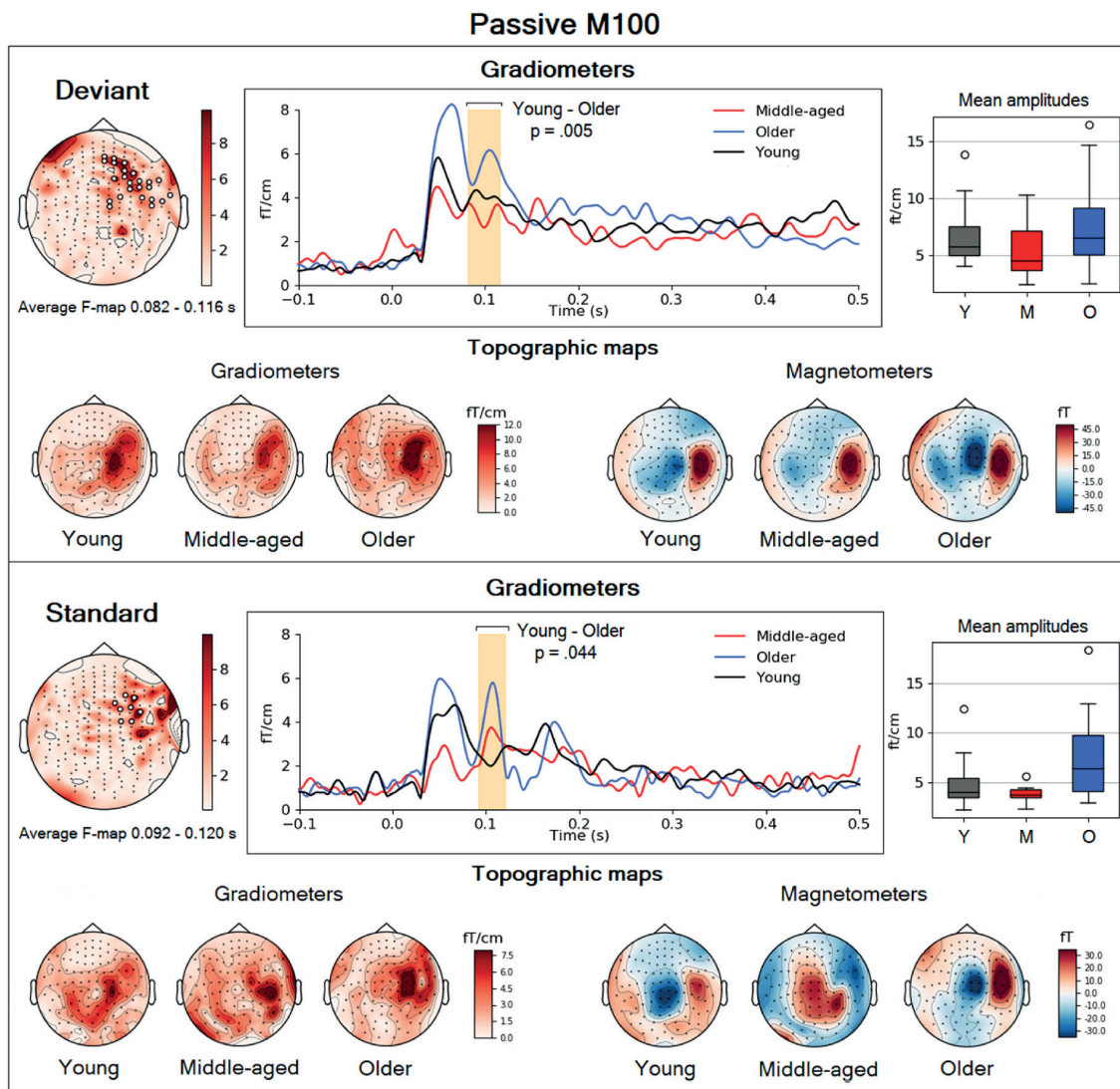
Fig. 2. Results for the M100 in the passive condition for deviant (above) and standard (below) stimuli. Significant clusters showing differences between young and older adults are represented by the highlighted dots in the topographic map (top left) with the red color representing the average F-value distribution. Grand averaged evoked responses for young (n = 12), middle-aged (n = 7), and older adults (n = 14) from the sensors of the significant clusters (RMS) are presented in the middle, with the yellow shaded area indicating the time window of the significant cluster. Mean amplitude values (absolute) for sensors and time window in the significant cluster for each group are presented in boxplots (right, Y = young, M = middle-aged, O = older). The horizontal line inside the boxes represents the median for each group. Topographic maps for each group's evoked response peak in the cluster time windows are presented separately for gradiometers (RMS, left) and magnetometers (right).

between the young and middle-aged groups.

*3.4. Comparison of M100 amplitude between active and passive condition*

The early M100 component with significant effects was also tested under active and passive conditions within the groups of young and older adults separately for standard and deviant stimuli. The spatio-temporal permutation test for magnetometers revealed a significant difference between the active and passive conditions for older adults – with larger amplitude values towards positive polarity in the active than in the passive condition – in 81 ms–110 ms time window for the deviant stimulus (p = .009) (Fig. 6). No differences were found in young adults.

4. Discussion

The aim of this study was to investigate how non-attended and

attended somatosensory brain processing may differ in young, middle-aged, and older adults. We recorded early sensory and later cognitive brain responses with MEG in passive and active oddball paradigms, in which electrical pulses were delivered to fingers. We found a larger M100 amplitude in older adults than young adults for standard stimuli in both passive and active conditions, as well as for deviant stimuli in the passive condition. Furthermore, the M250 in the passive condition was reduced in amplitude, and the M350 in the active condition was altered in older compared to younger adults. These results are discussed in detail below.

As expected, older adults presented a larger M100 amplitude than young adults. Here, we found a larger M100 amplitude not only for standard stimuli in both conditions, but also for deviant stimuli in the passive condition. The larger M100 for standard stimuli in older adults most probably reflects unsuccessful attenuation of cortical activity – that is, sensory gating, for repetitive stimuli. Decreased gating in older adults
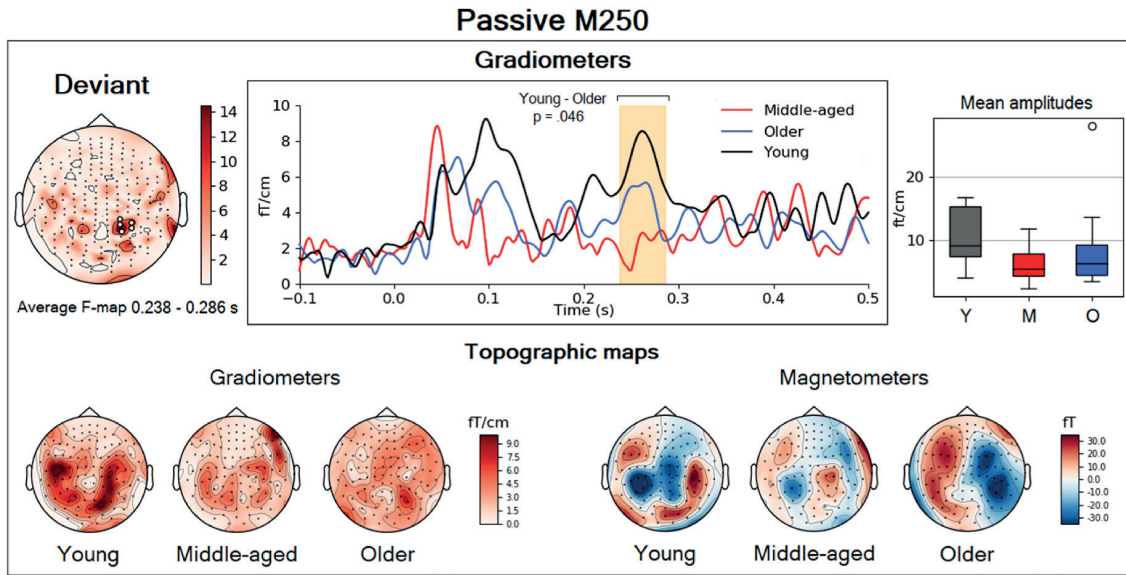
Fig. 3. Results for the M250 in the passive condition for the deviant stimulus (no significant cluster was found for the responses to the standard stimulus). Significant clusters showing differences between young and older adults are marked with the highlighted dots in the topographic map (top left) with the red color representing the average F-value distribution. Grand averaged evoked responses for young (n = 12), middle-aged (n = 7), and older adults (n = 14) from the sensors of the significant clusters (RMS) are presented in the middle with the yellow shaded area indicating the time window of the significant cluster. Mean amplitude values (absolute) for each group for sensors and time-window of the cluster are presented in boxplots (right, Y = young, M = middle-aged, O = older). Horizontal line inside the boxes represents median for each group. Topographical maps for each group's evoked response peak in the cluster's time windows are presented below for gradiometers (RMS, left) and magnetometers (right).
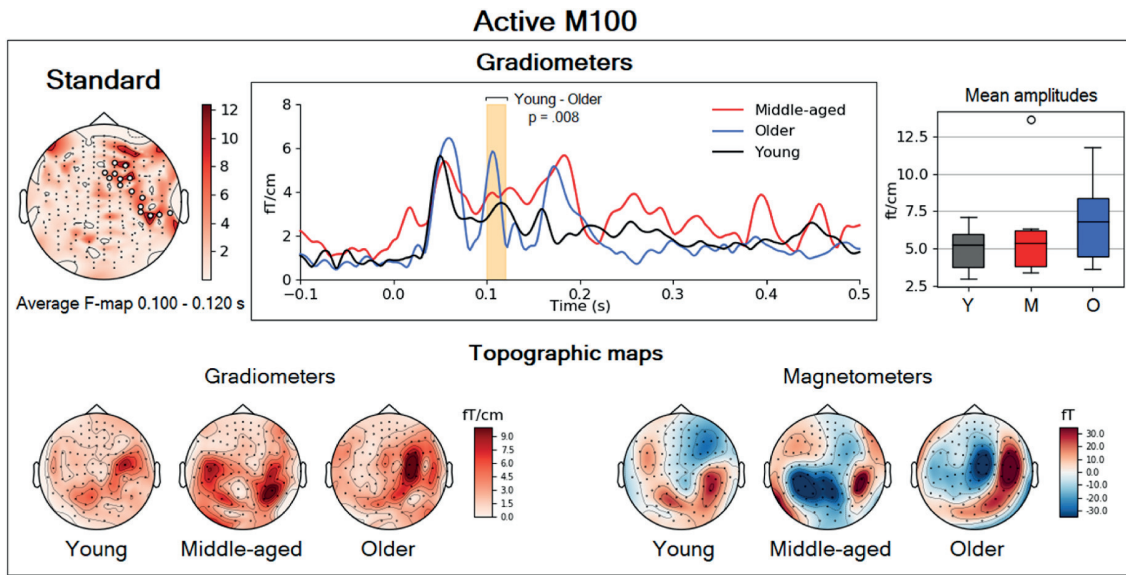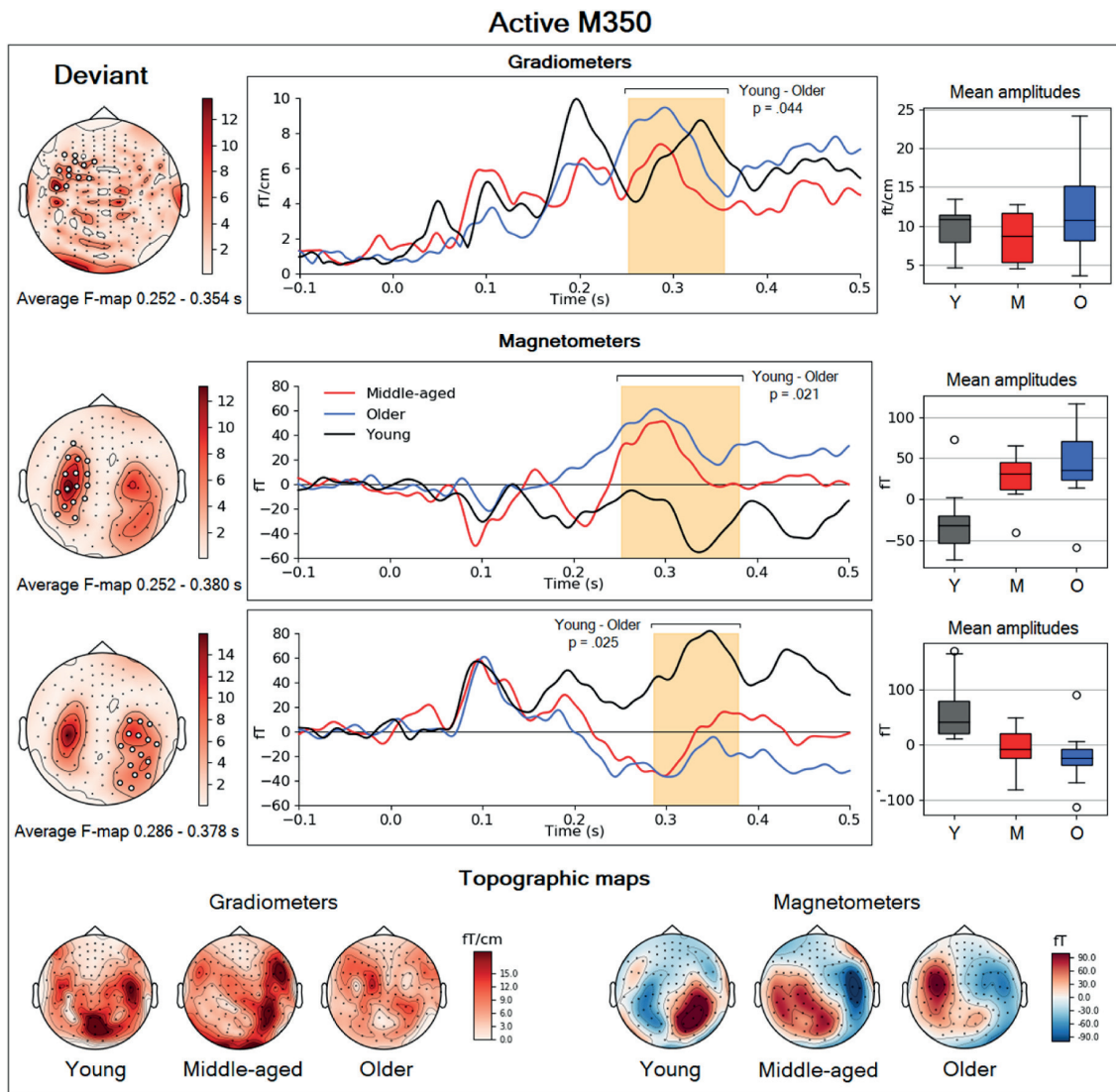

Fig. 4. Results for the M100 in the active condition for the standard stimulus (no significant cluster was found for the responses to the deviant stimulus). Significant cluster showing differences between young and older adults is represented by the highlighted dots in the topographic map (top left) with the red color representing the average F-value distribution. Grand averaged evoked responses for young (n = 12), middle-aged (n = 6), and older adults (n = 12) from the sensors of the significant cluster (RMS) are presented in the middle with the yellow shaded area indicating the time window of the significant cluster. Mean amplitude values (absolute) for each group for sensors and time-window of the significant cluster are presented in boxplots (right, Y = young, M = middle-aged, O = older). The horizontal line inside the boxes represents median for each group. Topographic maps for each group's evoked response peak in the cluster time window are presented below each cluster separately for gradiometers (RMS, left) and magnetometers (right).

compared to younger adults has also been reported in previous somatosensory EEG (e.g. Alain et al., 2022; Bolton and Staines, 2012; Terrasa et al., 2018) and MEG studies (Spooner et al., 2019). It is significant that larger amplitudes were detected in older than young adults for task-irrelevant stimuli (i.e., standard and deviant stimuli in the passive condition and standard stimuli in the active condition), but not for task-relevant stimuli (deviant stimuli in the active condition). Similar age-related findings of impaired suppression of task-irrelevant stimuli in early stages of stimulus processing have also been reported in auditory and visual modalities (Chao, 1997; Gazzaley et al., 2008;
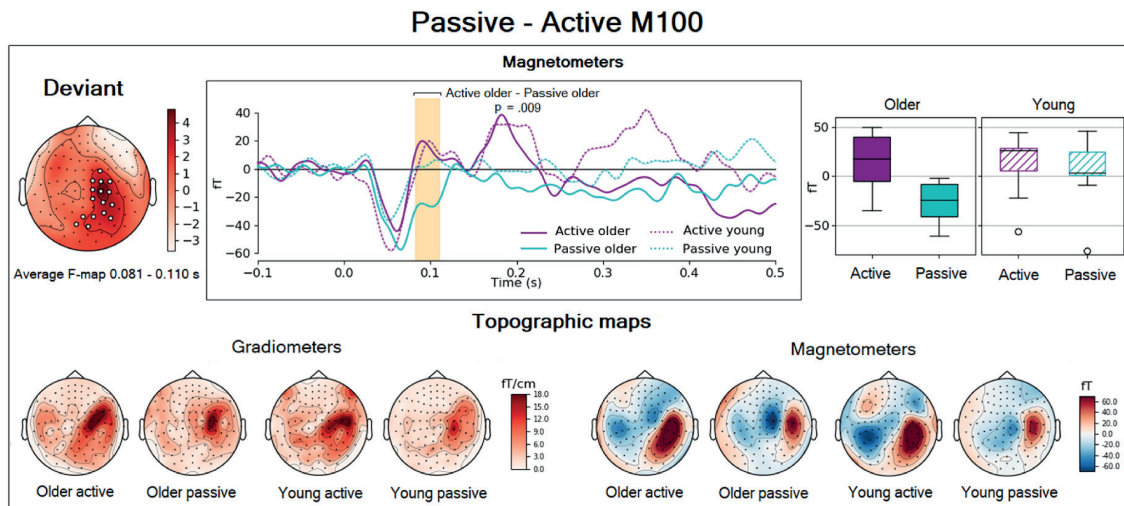
Fig. 5. Results for the M350 in the active condition for the deviant stimulus for gradiometers (above) and magnetometers (middle). Significant clusters showing differences between young and older adults are represented by the highlighted dots in the topographic map (top left) with the red color representing the average F-value distribution. Grand averaged evoked responses for young (black line, n = 12), middle-aged (red line, n = 7), and older adults (blue line, n = 14) from the sensors of the significant clusters (RMS for gradiometers) are presented in the middle with the yellow shaded area indicating the time window of the clusters. Mean amplitude values for each group for sensors and time-window of the significant clusters are presented in boxplots (right, Y = young, M = middle-aged, O = older). The horizontal line inside the boxes represents median for each group. Topographic maps for each group's evoked response are presented separately for gradiometers (RMS, left) and magnetometers (right).

Ruohonen et al., 2020; Stothart and Kazanina, 2016). Similar to our study, where M50 responses did not differ between groups, previous studies have not always found group differences in responses preceding M/P100 in the somatosensory modality (e.g. Bolton and Staines, 2012; Strömmer et al., 2017). In Strömmer et al. (2017), P50 and N80 elicited in EEG recordings were larger for both standard and deviant stimuli in older than younger adults, but the group difference was not found when the analysis was controlled for stimulus intensities, which were higher for the older than younger adults. However, Bolton and Staines (2012) found a difference in unattended standard P100 amplitudes between young and older adults, such that those of older adults were more positive than those of young adults. No difference was found for attended standard P100, in which attention was focused on standard stimuli. This finding supports the interpretation that the older adults exhibit reduced suppression of task-irrelevant stimuli outside of focus of attention.

When M100 responses were compared between active and passive

conditions in the present study, M100 amplitude to the deviant, but not to the standard stimulus, was found to be larger towards positive polarity in the active condition than in the passive condition in older adults; however, no such condition difference was found in young adults. In a previous study, Bolton and Staines (2012) found a reduction in attentional modulation of the P100 to the *standard* stimulus in older compared to younger adults. The authors interpreted this finding to reflect reduced suppression of non-attended stimuli in older subjects, but because they did not investigate the attention effect for deviant stimuli, it is not possible to directly compare the results of the two studies. It is possible that the deviant M100 in the present study also partly reflects deviance detection and not only sensory gating, because the components were not separated, for example, with independent component analysis (ICA, see e.g., Astikainen et al., 2013 for visual MMN). Therefore, our finding of a larger M100 in the active than in the passive condition in older adults may at least partly reflect impaired

Fig. 6. Results comparing M100 in the active and passive condition within the groups separately. The difference between the conditions was found only for the older adults, and in the in the deviant stimulus responses. Significant cluster showing differences between active and passive condition in older adults is represented by the highlighted dots in the topographic map (top left) with the red color representing the average F-value distribution. Grand averaged evoked responses for older (solid line, n = 12) and young adults (dashed line, n = 12) from the sensors of the significant cluster (RMS) are presented in the middle with the yellow shaded area indicating the time window of the significant cluster. Mean amplitude values for each group for the sensors and time-window of the cluster are presented in boxplots (top right). The horizontal line inside the boxes represents median for each group. Topographic maps for each group's evoked response peak in the cluster time window are presented separately for gradiometers (RMS, left) and magnetometers (right).

change detection in older adults, which can be improved by attention towards stimuli.

In our study, older adults also demonstrated poorer inhibitory abilities on cognitive tests – as indicated by performance on Stroop 1 and TMT-B (Alvarez and Emory, 2006; Linari et al., 2022) – than younger and middle-aged participants. Moreover, Stroop 3, which also measures inhibitory abilities, revealed lower scores in older than young adults; however, the result was only borderline significant. The loss of inhibitory control in ageing is likely due, at least in part, to a decline in pre-frontal cortex (PFC) function, which acts to suppress irrelevant information in the early stages of sensory processing (Yamaguchi and Knight, 1990). This has been demonstrated in studies in which both following continuous theta burst stimulation at dorsolateral PFC and in individuals with prefrontal lesions, loss of attention based modulation of early somatosensory processing has been demonstrated (Bolton and Staines, 2011, 2014). In our study, we did not perform a specific analysis on the PFC and therefore cannot state whether the differences we observed are due to PFC activity.

Regarding the later components, we found a difference in the M250 component between young and older adults in the passive condition, indicating a stronger activity in the parietal cortex contralateral to stimulation in young adults. The M250 component most likely corresponds to the P3a reported in passive oddball condition in EEG studies (Polich, 2007). P3a has been reported in somatosensory EEG studies at very similar latency ranges, 200 ms–300 ms after stimulus onset (Kangas et al., 2021; Shen et al., 2018; Strömmer et al., 2017), as in our MEG recording. P3a elicited in a passive oddball condition is suggested to reflect an automatic re-orienting of attention toward the deviant stimulus (Polich, 2007). Predictive coding theory, which has been proposed to explain the brain responses to deviance detection (Friston, 2005; Garrido et al., 2009), has been linked to both MMN and P3a elicitation. While MMN is suggested to reflect prediction error, P3a has been associated with a transient expression of prediction error within predictive coding theory (Friston, 2005). The most crucial neural networks generating P3a across different sensory modalities are suggested to be located in the frontal lobe, hippocampus, and anterior cingulate cortex (Friedman et al., 2001; Knight, 1996; Wronka et al., 2012). Our topographic maps suggested centro-parietal activity in this latency window,

especially in young adults, whereas the activity was shifted more towards the frontal areas in older adults. Our results from the passive oddball condition suggest, that the attention-shifting mechanism toward changes is altered in older adults. In our previous ERP study, we did not identify any amplitude difference between young and older adults in the somatosensory P3a (Strömmer et al., 2017). This discrepancy may be related to the different methodology in these studies, as the recording here was based on a MEG method; however, further studies are required to confirm this.

Surprisingly, we found no significant difference between groups within the MMN latency range. Our previous ERP studies have identified differences between younger and older adults for the somatosensory MMR, in the latency ranges of 153 ms–193 and 250 ms–290 ms (Strömmer et al., 2014, 2017). There is also evidence of decreased auditory MMN amplitudes in older adults compared to young adults (Cheng et al., 2013; Ruzzoli et al., 2012). The MMN and sMMR are theorized to reflect predictive coding and prediction error (Friston, 2005; Naeije et al., 2016; Wacongne et al., 2012; Xu et al., 2021). Previous studies have suggested that the brain's predictive coding of sensory information and working memory is impaired in older adults (Cheng et al., 2013; Ruzzoli et al., 2012; Strömmer et al., 2014, 2017). One possible mechanism could be the age-related decline in sensory gating of repetitive (standard) stimuli, which affects the higher-order predictive coding of the rare, deviant stimuli – also observed as M100 enhancement in this study. Furthermore, the N-methyl-D-aspartate (NMDA) receptor is shown to decline with ageing (Müller et al., 1994), which has been found to contribute in predictive coding of sensory input and MMN production (Wacongne et al., 2012). The reason for the absent group differences in the present study is unknown, but it is possible that the MEG or analysis procedure chosen here does not image the neural populations eliciting the MMR very well; moreover, it is also possible that the sample size or the analysis method of the present study is not sufficient to detect small effects (however, the sample size is not much larger in Strömmer et al., 2014, who identified the group difference in the sMMR in an EEG measurement). Furthermore, we analysed the deviant and standard responses rather than the difference waves, as the signal-to-noise ratio is poorer in difference responses, and such an analysis cannot define whether the group differences are related to

standard or deviant stimuli (see e.g. Kremláček et al., 2016). Rather, the group differences in the somatosensory P3a observed here may reflect the neural deficits of predictive coding in the later stage of automatic deviance detection, as discussed above. Further studies of somatosensory MMR and P3a in older adults are needed, as very few studies have been undertaken in this modality in older populations.

In the active condition, our results revealed a difference between young and older adults in M350, which corresponds to P3b in the EEG literature. P3b, elicited in an active oddball condition, is associated with attention, decision making and working memory updating (for a review, see Polich, 2007). Older adults differed from young adults in both gradiometer and magnetometer activity. We included the analysis of magnetometers because they record a slightly different activity compared to gradiometers. While gradiometers typically reveal neural activation immediately beneath the sensor, magnetometers show magnetic polarity, which describes the direction of the electric current in cortical neurons (Baillet, 2017). Further inspection of the effect found with the spatiotemporal permutation test and group topographies suggested that the activity was more parietally and occipitally pronounced in young adults than older adults, whose topographies indicated more frontally pronounced activity. This effect suggests that the M350 activity is shifted towards frontal areas in older adults, and previous evidence from P3b ageing studies supports this interpretation (Alperin et al., 2014; Dinteren et al., 2018; Reuter et al., 2017). In young adults, a large number of neural generators found to contribute to P3b generation across modalities are located mainly in the parietal and cingulate cortices (Linden, 2005). Particularly in the somatosensory domain, for example, the bilateral temporoparietal, hippocampal or para-hippocampal, thalamic, and supplementary motor area have been identified as sources of P3b (Huang et al., 2005; Naeije et al., 2016; Tarkka et al., 1996).

More frontally pronounced activity in P3b in older adults is known as the frontal shift in the P3 literature, but its origins are not clear (Dinteren et al., 2014b). Recently, principal component analyses exhibiting an overlap and co-occurrence of the early frontal P3 wave with the more parietally located P3b wave have suggested that the frontal P3a contributes to P3 activity in the attended oddball paradigm as well (Alperin et al., 2014; Kamp, 2020). Therefore, P3a – a sub-component indicating stimulus evaluation and attention interruption processes – has been suggested to co-occur with P3b in both young and older adults. In these studies, young adults have shown a much smaller frontal P3 wave than parietal P3b, whereas older individuals have shown similar amplitudes of both components (Alperin et al., 2014; Kamp, 2020). Our frontal grand average waveform shows a rather early peak around 300 ms after stimulus onset in older individuals, compared to parietally found activity, which may reflect the early P3a activity. However, we did not perform specific principal component or source analysis to be able to confirm this observation.

The functional significance of the age-related frontal shift in P3b remains under debate. It has been theorized to arise from compensational processes – that is, frontal compensation – in which additional brain areas are suggested to be utilized for better cognitive function (Alperin et al., 2014; Cabeza et al., 2018; Dinteren et al., 2018). This theory has recently been questioned by Kamp (2020), who found no correlation with frontal activity and target recognition, which by contrast was found to be associated with parietally recorded P3b amplitudes. As a result, the abovementioned study suggested that enhanced frontal activity may indicate that older adults simply recruit more complex cognitive control for task execution. In our study, we did not find any differences between the groups in target recognition or reaction times. These theories require further research to clarify the functional significance of the enhanced activity in the frontal regions in ageing. Overall, P3b has been found to correlate with several cognitive abilities, such as memory and processing speed (Polich, 2007). In our study, older adults exhibited poorer performance on cognitive tests for both abilities in multiple different tests (e.g. RAVLT, ROCF-test, logical memory

delayed, digit-span backwards, LNS, and TMT-A).

4.1. Limitations

The present study has certain obvious limitations. Our overall sample size remained quite small, which might have affected our results especially for the middle-aged adults. On visual inspection, the grand average waveforms for significant clusters for M350 showed a similar activity pattern in magnetometers for middle-aged and older adults. It may be that middle-aged adults already show changes in attended deviant processing compared to young adults, but our sample was too small to detect this difference. This study should therefore be repeated with a larger sample. We also limited our analysis here to sensor level, and did not perform source analysis, as we did not have magnetic resonance imaging data of the participants' brain structure. The main research question was not to search for sources of the activity, although the results suggest that there may also be certain source differences between the groups in the analysed responses. The sources of somatosensory MMR and non-target oddball responses with similar latencies have been connected to SII in many studies (Akatsuka et al., 2007; Hautasaari et al., 2018; Kida et al., 2007; Naeije et al., 2016, 2018; Xu et al., 2021). Further studies with source localization should be performed in older adults. It should also be noted that the analysis was based on a whole head model, which might hide small effects that are limited to a small group of sensors.

4.2. Conclusions

Our results suggest an age-related modulation of somatosensory brain function in both non-attentive and attentive processing. The detected changes indicate attenuated sensory gating (M100) and altered attentional processes (M250 and M350) in older adults compared to young adults. These brain responses should be further studied in healthy and diseased ageing since they might have potential for clinical applications in early detection of cognitive decline.

Author Contributions

Data availability

Data will be made available on request.

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