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Juho Strömmer

Brain, Cognition and Physically Active Lifestyle in Healthy Ageing

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ABSTRACT

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Normal ageing is accompanied by profound changes in brain structure and declines in the automatic processing of sensory stimuli, which in turn lead to altered cognitive performance. However, behaviour and lifestyle factors, such as physical activity, may help to maintain the brain's structural connectivity and function, as well as cognitive functioning in old age. Study I examined the effects of age on the brain's capability to detect changes in somatosensory stimuli by recording event-related potentials (ERPs) in response to electrical stimulation of different fingers in young and older adults. The results of Study I show that somatosensory mismatch response (sMMR) was attenuated in amplitude in older subjects as compared to young adults, indicating age-related decline in somatosensory change detection. Study II investigated whether age-related decline in the change detection mechanism in somatosensory and auditory modalities is associated with age-related alterations in cognitive performance, and whether physical fitness modulates this relationship. The results of Study II showed that the higher the sMMR amplitudes were the better executive functions older adults had. In addition, better aerobic fitness was linked to higher somatosensory ERP amplitudes and to better executive functions. Study III examined whether physical activity mediates the effect of age on the brain's white matter integrity, and whether, in tracts sensitive to physical activity, this integrity mediates age-related decline in cognitive speed and fluid cognitive capabilities. The results of Study III show that overall daily physical activity mitigates age-related decline of white matter integrity. In addition, physical activity that benefits white matter integrity in the genu of the corpus callosum is associated with reduced ageing-related slowing of reaction times. Overall, these results indicate that age-related changes in the brain's electrophysiological responses are linked to changes in cognitive performance, and that a physically active lifestyle protects against age-related structural disconnection and cognitive slowing, as good aerobic fitness helps to preserve physiological and executive functions in ageing.

Keywords: aging, cognitive decline, event-related potential, physical activity, physical fitness, white matter

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Ikääntyessä aivoissa tapahtuu rakenteellisia muutoksia ja kyky käsitellä aisti-informaatiota muuttuu, mikä johtaa muutoksiin tiedonkäsittelytoiminnoissa. Toisaalta elämäntavoilla, kuten fyysisellä aktiivisuudella, voi olla aivoja suojaavia ja toimintaa ylläpitäviä vaikutuksia myös ikääntyessä. Tämän väitöskirjan ensimmäisessä osatutkimuksessa selvitin ikääntymisen vaikutuksia aivojen kykyyn havaita muutoksia aistiympäristössä mittaamalla aivovasteita eri sormiin annettuihin sähköisiin tunto-ärsykkeisiin terveillä nuorilla ja ikääntyneillä aikuisilla. Tutkimuksessa osoitettiin ensimmäistä kertaa, että muutoksenhavaitsemisvaste tuntoaistijärjestelmässä oli ikääntyneillä nuoriin verrattuna heikentynyt. Seuraavassa osatutkimuksessa tutkin muutoksen havaitsemiseen liittyvien tunto- ja kuuloaivovasteiden ja kognitiivisten kykyjen yhteyttä nuorilla ja ikääntyneillä. Lisäksi selvitin aerobisen kunnon yhteyttä aivovasteisiin ja kognitiiviseen suoriutumiseen ikääntyneillä. Tulokset osoittivat, että ikääntyneillä voimakkaampi muutoksenhavaitsemisvaste tuntoaistijärjestelmässä oli yhteydessä parempaan suoriutumiseen toiminnanohjausta vaativissa tehtävissä. Nuorilla voimakkaampi muutoksenhavaitsemisvaste kuuloaistijärjestelmässä oli yhteydessä parempaan suoriutumiseen työmuistitehtävissä. Hyvä aerobinen kunto puolestaan oli ikääntyneillä yhteydessä hyvään toiminnanohjauskykyyn sekä suurempiin tuntoaistijärjestelmän herätevasteisiin. Kolmannessa tutkimuksessa selvitin, voiko fyysinen aktiivisuus jarruttaa ikääntymisen aiheuttamaa rappeutumista aivojen valkeassa aineessa. Lisäksi selvitin, voiko valkean aineen suurempi tiheys fyysisestä aktiivisuudesta hyötyvillä aivoalueilla jarruttaa ikääntymiseen liittyvää kognitiivista hidastumista sekä joustavien taitojen heikkenemistä. Tutkimus osoitti, että fyysinen aktiivisuus jarruttaa ikääntymiseen liittyvää valkean aineen rappeutumista. Lisäksi eheämpi valkea aine aivokurkiaisen etuosassa, missä myös fyysisen aktiivisuuden vaikutukset ovat voimakkaita, on yhteydessä pienempään ikääntymiseen liittyvään hidastumiseen. Väitöskirjan tulokset osoittavat, että ikääntymiseen liittyvät muutokset aivojen automaattisissa herätevasteissa ovat yhteydessä ikääntymiseen liittyviin muutoksiin kognitiivisissa toiminnoissa. Lisäksi fyysinen aktiivisuus ja hyvä fyysinen kunto voivat jarruttaa ikääntymiseen liittyvää aivojen rappeutumista ja aivotoiminnan muutoksia sekä suojata kognitiiviselta hidastumiselta.

Asiasanat: ikääntyminen, kognitiivinen heikkeneminen, herätevasteet, fyysinen aktiivisuus, fyysinen kunto, valkea aine

FOREWORD

Scientific research is not possible to implement alone. Nor can one's thinking develop without interaction with other minds. First of all, I wish to thank my supervisor, scientific mentor and friend Piia Astikainen for her dedicate guidance and patience throughout my academic journey. Thank you Piia for infecting your passionate and inspiring attitude towards science and for creating such a pleasant working atmosphere for us! You are the heroine of this dissertation. I am also very grateful to my supervisor Ina Tarkka for her encouragement towards academic career and for sharing her expertise and inspiring ideas during my doctoral studies. Furthermore, I wish to thank the reviewers of the dissertation, Professor Minna Huotilainen and Adjunct Professor Kiti Müller for the time and expertise they have dedicated to make this thesis better. I am also thankful to all of the co-authors of the research papers composing this dissertation, to Ville Kirjavainen for his enormous contribution to data collection management, to Petri Kinnunen, Lauri Viljanto and Jarno Mikkonen for the technical assistance, and to all of the students that have been involved in the research. Joona Muotka also deserves an acknowledgement for his kind help in statistical issues. I wish to thank all the participants of the studies who have dedicated their time for science. Obviously, this work would not have been possible without all of you.

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Taking into account the instructions given and comments made by the co-authors, the author of the thesis conducted the data analyses and wrote the reports for the three publications. In Studies I and II, the author participated in designing the study and played a significant role in stimulus preparation, data collection and coordination. In Study III, he was privileged to utilize previously collected data.

FIGURES

TABLES

CONTENTS

1 INTRODUCTION

Normal ageing is accompanied by profound changes in brain structure (Raz et al., 2005), including grey matter atrophy and decreases in white matter integrity (Bennett, Madden, Vaidya, Howard, & Howard, 2009; Madden et al., 2012; Salami, Eriksson, Nilsson, & Nyberg, 2012). These structural changes eventually result in reorganisation of neural circuits, compensatory brain activity and changes in neural transmission, leading in turn to changes in cognitive performance (Grady, 2012; Reuter-Lorenz & Park, 2010). In other words, changes in the nervous system precede those in behaviour. Just as certain cognitive abilities can be acquired only after adequate brain maturation in childhood, certain cognitive abilities may diminish in the later years of life as a result of brain tissue degeneration. However, behavioural and life style factors such as exercise and physical activity may improve brain plasticity, helping to maintain and even enhance brain structure and function (Gow, Bastin, et al., 2012; Duzel, van Praag, & Sendtner, 2016; Voelcker-Rehage & Niemann, 2013), and cognitive functioning (Davenport, Hogan, Eskes, Longman, & Poulin, 2012) in old age.

The aim of the present research was to investigate the effect of normal ageing on the brain's fundamental capability to detect changes in sensory stimuli, and to test the association between these changes and age-related changes in cognitive performance, and their relation to physical fitness. The research also examined whether physical activity mediates the detrimental effects of ageing on white matter integrity and, in turn, the hypothesised mediating effects of white matter integrity on processing speed and fluid capabilities. The dissertation's overarching objective was to examine links between the neural basis of human cognitive ageing and relevant behavioural factors (Figure 1).

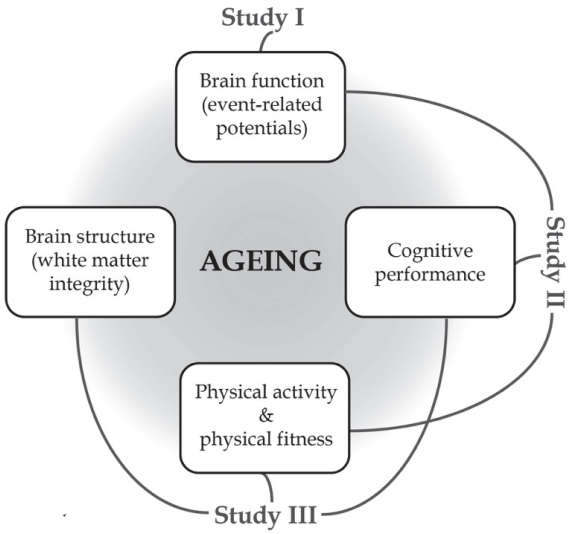

FIGURE 1 Schematic overview of the research.

1.1 Change detection mechanism and cognitive ageing

In daily life, a vast number of environmental stimuli bombard our sensory systems. However, we pay attention to only a small proportion of that sensory input (Damasio, 1995); by filtering out irrelevant incoming sensory information, more resources can be reserved for information that is presumed to be relevant. It is thought that the brain is capable of learning rapidly and effortlessly to detect regularities in the environment and to predict what is likely to happen in the future (Wacongne, Changeux, & Dehaene, 2012). Because these predictions are constantly updated based on new input, the brain can detect sudden changes in the environment, even without deploying attentional resources.

In laboratory settings, sensory change detection can be operationalised as a simple paradigm, in which continuous stimuli are interspersed with deviations in the rule of regularity (Figure 2). This so-called 'oddball' paradigm might, for instance, involve violations in sound frequency, intensity, duration or location, and electroencephalographic recording can capture mismatch negativity (MMN) (Näätänen, Gaillard, & Mäntysalo, 1978; for a review, see Näätänen, Astikainen, Ruusuvirta, & Huotilainen, 2010). Originally the MMN is interpreted as a change detection response based on a comparison of memory traces formed by standard stimuli and a deviant stimulus input (Näätänen & Alho, 1995). Another, more recent interpretation is related to a predictive coding of the stimulus environment (Garrido, Kilner, Stephan, & Friston, 2009; Wacongne et al., 2012; Winkler & Czigler, 2012). In addition to auditory changes, the MMN response is also elicited by changes in somatosensory (Akatsuka et al.,

2005; Kekoni et al., 1997; Restuccia et al., 2009; Shinozaki, Yabe, Sutoh, Hiruma, & Kaneko, 1998; Spackman, Towell, & Boyd, 2010), visual (Astikainen, Lillstrang, & Ruusuvirta, 2008; Kimura, Schröger, Czigler, & Ohira, 2010), and olfactory (Pause & Krauel, 2000) stimuli.

In older age, the brain's ability to detect changes and make predictions about events in the environment gradually declines (Kiang, Braff, Sprock, & Light, 2009; Ruzzoli, Pirulli, Brignani, Maioli, & Miniussi, 2012). These age-related alterations in change detection have mostly been studied in relation to the auditory sensory modality in cross-sectional settings, comparing the brain responses of different age groups (for a review, see Cheng, Hsu, & Lin, 2013; see also Näätänen et al., 2011). Typically, the amplitude of the auditory MMN (aMMN) response to changes in sound frequency (Alain & Woods, 1999; Cooper, Todd, McGill, & Michie, 2006; Gaeta, Friedman, Ritter, & Cheng, 1998), duration (Cooper et al., 2006; Kiang et al., 2009) and inter-stimulus interval (Ruzzoli et al., 2012) is attenuated in older adults as compared to younger subjects. Additionally, aMMN latency appears to be prolonged with ageing (e.g. Bertoli, Smurzynski, & Probst, 2002; Gaeta, Friedman, Ritter, & Cheng, 2001).

While there is relatively little research on the effects of normal ageing on change detection mechanism in sensory modalities other than audition, a few studies have reported altered visual MMN amplitudes for changes in visual stimuli among healthy older adults as compared to young adults (Tales & Butler, 2006; Tales, Troscianko, Wilcock, Newton, & Butler, 2002). In the somatosensory sensory modality, the change detection mechanism is known to decline in cases of mild cognitive impairment and neurodegenerative disease (for reviews, see Näätänen et al., 2012; Näätänen et al., 2011). To my knowledge, however, the effects of normal ageing on change detection in the somatosensory modality have not yet been investigated.

As changes in the nervous system constantly interact with changes in behaviour, event-related potentials (ERPs) are a refined tool for detecting early phase ageing changes in sensory-cognitive functions before they are discernible in behaviour (Rossini, Rossi, Babiloni, & Polich, 2007). The ageing brain can compensate for neural challenges by means of enhanced frontal recruitment, increased distribution and bilaterality of processing, which can be further enhanced through learning, exercise and cognitive training (Reuter-Lorenz & Park, 2010). With compensation of this kind, the effects of ageing on behaviour may appear delayed in relation to neural changes in the brain. In healthy older adults, the higher amplitude of aMMN responses to changes in sound duration have been linked to better executive functions and verbal memory (Foster et al., 2013), and age-related decrease of aMMN amplitude in response to inter-stimulus interval deviation has been shown to be associated with the decline of executive functions in healthy ageing (Kisley, Davalos, Engleman, Guinther, & Davis, 2005).

In addition to MMN, other components of auditory ERPs, namely N1, P2, and P3a, are also known to be sensitive to normal ageing (Crowley & Colrain, 2004; Friedman, Cycowicz, & Gaeta, 2001; Tome, Barbosa, Nowak, & Marques-

Teixeira, 2015). These ERPs are automatically elicited even when the participant's attention is directed away from the stimuli, indicating different hierarchical phases of cortical sensory processing. The response amplitude of the auditory N1, which presumably reflects early automatic stimulus encoding (Näätänen, 1990), has been reported to increase for repetitive standard stimuli in older adults, supposedly indicating an age-related decrease in sensory inhibition (Stothart & Kazanina, 2016). P2, which is involved in stimulus classification and processing of task-irrelevant stimuli (García-Larrea, Lukaszewicz, & Mauguière, 1992; Novak, Ritter, & Vaughan, 1992), is reported to decrease in amplitude with ageing, presumably reflecting less efficient automatic registration of these stimuli in older adults (Czigler, Csibra, & Csontos, 1992). The ERP component P3a reflects the automatic re-orienting of attention that follows pre-attentive change detection and may also include conscious stimulus recognition (Friedman et al., 2001) Like MMN, auditory P3a typically decreases in amplitude in normal ageing (Gaal, Csuhaj, & Molnar, 2007; Kiang et al., 2009; Knight, 1987), with longer latency (Gaeta, Friedman, Ritter, & Cheng, 2001), probably indicating age-related deterioration of the attention-switching mechanism (Friedman et al., 2001). In the somatosensory modality, P3a is elicited by means of an oddball paradigm in the same way as auditory P3a (Butler et al., 2011; Spackman, Boyd, & Towell, 2007), although the oddball paradigm is rarely used in somatosensory ageing studies.

1.2 White matter integrity and age-related cognitive decline

About 40–50% of brain tissue consists of white matter— the capillary blood vessels, and the myelinated axons that organise communication between brain regions, so coordinating cognitive performance, which is dependent on widely distributed neural systems. White matter microstructure declines gradually with age throughout the brain, and this decline accelerates in old adulthood (> 60 years), especially in the frontal associative tracts (Guttmann et al., 1998; Madden, Bennett, & Song, 2009; Raz et al., 2005). These changes are driven mainly by atrophy in the oligodendrocytes that form the myelin shield around axons, and by the loss of thin neural fibres (Madden et al., 2009; Marner, Nyengaard, Tang, & Pakkenberg, 2003). The decline in white matter microstructure reduces the efficiency of communication among brain regions, contributing to cognitive decline in ageing (Bennett & Madden, 2014; Madden et al., 2009; Salat, 2011).

Fractional anisotropy (FA) is an index of microstructural white matter integrity; by assessing the directional selectivity of random diffusion of water molecules in the tissue, FA indirectly measures the myelin level in the white matter (Beaulieu, 2002). High FA values commonly indicate high myelination of axons (i.e. high diffusivity parallel to axon fibres, with low transverse diffusivity); low FA values are likely to indicate low myelination of axons (i.e. high randomness of direction of diffusivity) (Beaulieu, 2002; Kochunov et al.,

2012). In normal ageing, FA declines progressively, especially in frontal white matter tracts that are myelinated late in life, such as anterior parts of the corpus callosum (Kochunov et al., 2012; Salat et al., 2005).

Loss of white matter myelin integrity and the consequent cortical disconnection is thought to be among the essential mechanisms underlying normal age-related cognitive decline and variability in cognitive performance (Bennett & Madden, 2014; Madden et al., 2012, 2009). Recent research shows that higher FA values correlate positively with better performance in cognitive domains that are susceptible to decline with normal ageing, including fluid intelligence, executive functions and processing speed (Bennett & Madden, 2014; Gazes et al., 2015; Nilsson, Thomas, O'Brien, & Gallagher, 2014), as well as in very old age (Lövdén et al., 2014). Additionally, a sizeable proportion of age-related variation in cognitive processing speed has been shown to be attributable to decreases in white matter integrity, specifically in frontal regions (Kochunov et al., 2010; Madden et al., 2009). In particular, the effect of age on cognitive processing speed is known to be mediated by FA in the genu of the corpus callosum (Salami et al., 2012). In a recent study of a population-based sample of healthy adults, white matter integrity (i.e. FA) predicted individual differences in cognitive processing speed, which in turn predicted a majority of the variance in fluid capabilities (Kievit, Davis, Griffiths, Correia, & Henson, 2016). It seems, then, that maintenance of white matter structural connectivity may be critical for the prevention of general age-related cognitive slowing, and indirectly for preventing decline in higher cognitive functions that may benefit more from compensatory brain activation and behaviour in ageing (Reuter-Lorenz & Park, 2010).

1.3 Physical activity, physical fitness and cognitive ageing

The global population is progressively ageing (He, Goodkind, & Kowal, 2016; United Nations, 2015). At the same time, working life and daily life styles are becoming less physically active, which is considered a key risk factor worldwide for health and healthy ageing (WHO, 2009, 2015). Conversely, physical activity can attenuate (and even eliminate) the increased risk of all-cause mortality and diseases related to physical inactivity, including in old age (Ekelund et al., 2016; Hupin et al., 2015). In addition, prospective studies show that even low levels of physical activity provide significant protection against normal ageing-related cognitive decline and dementia (Blondell, Hammersley-Mather, & Veerman, 2014; Sofi et al., 2011) and Alzheimer's disease (Hamer & Chida, 2009; see also Larson et al., 2006). In fact, higher levels of physical activity are known to be associated with higher general cognitive ability and cognitive processing speed in late adulthood, regardless of social class or general intelligence scores at adolescence (Gow, Corley, Starr, & Deary, 2012). Similarly, it is well established that exercise and even small increases in aerobic fitness are beneficial to cognitive performance and especially to executive

functions in older adulthood (Colcombe & Kramer, 2003; Guiney & Machado, 2013; Kramer et al., 1999).

The benefits of physical activity and exercise for cognitive functioning are likely to be mediated by enhancements in brain structure and brain activation. Interestingly, Raichlen and Alexander (2017) have recently proposed that normal ageing-related neural atrophy is an adaptive response to the lower energy demands of a sedentary life style, and that a lack of stimulation affords the brain an opportunity for energy saving through capacity reduction, which is expressed as age-related neural atrophy. They propose that physical activity may to the same extent protect the brain from energy-saving atrophy, enhancing neuroplasticity across the life span. Indeed, an association has been identified in healthy older adults between engagement in physical activity, less neural atrophy and less decline in cerebral white matter integrity (Gons et al., 2013; Gow, Bastin, et al., 2012a). In addition, to preserve white matter health later in life, it may be important to avoid sedentary behaviour (Burzynska et al., 2014), given that a sedentary lifestyle is also more likely to be associated with obesity and poor aerobic fitness, which are in turn associated with lower white matter integrity (Marks, Katz, Styner, & Smith, 2011). However, few if any studies to date have examined the relationship between age-related decline in white matter integrity and total daily physical activity energy expenditure in population-based samples over the adult life span.

As in the case of physical activity, objectively high measured cardiorespiratory fitness is known to be positively associated with higher white matter integrity in late adulthood (for a review, see Sexton et al., 2015), especially in the genu of the corpus callosum (Johnson, Kim, Clasey, Bailey, & Gold, 2012). Prospective aerobic exercise intervention studies also show that better aerobic fitness among older adults is linked to increased white matter integrity in the prefrontal and temporal cerebrum (Voss et al., 2013) and to increased white matter volume in the anterior corpus callosum (Colcombe et al., 2006). Notably, these brain regions are particularly susceptible to progressive neural atrophy in normal ageing.

Most studies of physical fitness, the brain and age-related cognitive decline use magnetic resonance imaging-based methods and, to my knowledge, no ageing study has yet combined measurement of the brain's electrophysiological responses (i.e. ERPs) with objective measures of physical fitness, behaviour and cognition. However, higher physical activity is known to be associated with increased speed of cognitive processing in older adults, as well as with increased amplitude of ERP components related to stimulus encoding and attention switching (i.e. N1 and P3) (Chang, Huang, Chen, & Hung, 2013). Similarly, the less efficient performance of physically inactive older adults on a simple sound frequency deviation task as compared to those who are more active is associated with increased frontal activity (i.e. higher P3a amplitude), suggesting a stronger involuntary shift of attention towards task-irrelevant stimuli in inactive older adults (Getzmann, Falkenstein, & Gajewski, 2013). Additionally, in active older adults (but not in those who are passive),

ERPs related to attention switching (i.e. P3b) have been reported to be similar to the brain responses of young adults, although there is no known association with behavioural or cognitive measures (McDowell, Kerick, Santa Maria, & Hatfield, 2003).

1.4 Aims of the research

The present dissertation investigated the effects of ageing on cognitive processing and on brain structure and function. Three studies targeting age-related changes in cortical sensory processing and structural connectivity and how cognitive functioning relates to physical fitness and activity made it possible to examine different layers of cognitive ageing, their neural basis and the relationships between these layers. Specifically, the aim was to test age-related changes in brain structure (i.e. white matter integrity), brain function (i.e. cortical sensory processing measured as ERPs), behaviour (i.e. cognitive performance), and the associations between these and physical activity and fitness in normal human ageing.

Study I examined whether normal ageing has an effect on somatosensory change detection mechanism by comparing the brain responses of healthy young and older adults, using electrical pulses to different fingers. Based on earlier findings related to auditory sensory modality (Cheng et al., 2013), we expected to find diminished sMMR amplitude in older adults as compared to young adults. To my knowledge, this was the first study to investigate the effects of normal ageing on the somatosensory change detection mechanism.

Using a larger sample of young and older adults, **Study II** then examined whether possible age-related decline in somatosensory and auditory change detection mechanisms is associated with age-related decline in cognitive performance. This study also investigated whether better physical fitness is associated with less alteration in brain responses and better cognitive performance in older adults. It was hypothesized that both sMMR (Strömmer, Tarkka, & Astikainen, 2014) and aMMN amplitude (Cheng et al., 2013) would be attenuated in in older as compared to younger adults, and that ERP amplitudes would correlate with cognitive test scores (Foster et al., 2013; Kisley et al., 2005). In addition, we hypothesized that, as in the case of aMMN and sMMR, the ERP components P2 and P3a would be attenuated in older as compared to younger adults (Czigler et al., 1992; Kiang et al., 2009). It was also anticipated that better physical fitness would be associated with better cognitive performance and less alteration in ERP responses (Davenport et al., 2012; Duzel et al., 2016).

Study III examined whether physical activity mediates the effect of age on white matter integrity in particular tracts of the cerebrum, and whether these are the tracts most vulnerable to age-related decline. The study also investigated whether age-related slowing of reaction times and decline in fluid intelligence are mediated by white matter integrity in those tracts that benefit

from physical activity. To this end, we first tested the effect of age on physical activity, white matter integrity, reaction time and fluid intelligence within a healthy, population-based sample covering the adult lifespan. To my knowledge, this is the first study to examine the relationship between white matter health and participants' reports on everyday physical activities and routines (e.g. chores and getting to work), offering an ecologically valid counterpoint to standard intervention studies.

2 METHODS

2.1 Participants

The participants included three different samples of healthy adults: 36 healthy young and older adult Finns in **Study I**; 131 healthy young and older adults Finns in **Study II**; and a population-representative sample of 708 healthy English people in **Study III**. All participants in **Studies I** and **II** were right-handed and had no history of neurological disease or brain operations. In **Study III**, all participants were again right-handed; other exclusion criteria included poor vision, poor hearing, low MMSE (24 or lower on Mini-Mental State Examination = cognitive decline and elevated risk of neurodegenerative diseases) (Folstein et al., 1975), self-reported substance abuse, poor English knowledge, current psychiatric disorder or neurological disease. People with contraindications to magnetic resonance imaging (MRI) or magnetoencephalography (MEG) were also excluded. Table 1 summarises the samples and methods.

For **Study I**, 22 young and 14 older adults were recruited from a university students' email list and from a local organisation for retired people, respectively. After discarding those with disrupted electroencephalography (EEG) data (e.g. excessive movement during recording), the final analyses included data from 18 young adults (age range = 22–29; mean = 25; standard deviation, SD = 2.0; six female) and 13 older adults (66–95 years old, mean = 75 years, SD = 8.3, nine female).

The sample for **Study II** included 41 young adults and 90 older adult females. Young adult participants were recruited from the University of Jyväskylä students' association mailing lists, and older participants were recruited from the University of the Third Age in Jyväskylä and from the Society of the Retired in Jyväskylä, as well as by means of an announcement in the local newspaper. Sampling for **Study II** was conducted in two phases. For the 2013 data collection, participants were recruited for a larger study

investigating the effectiveness of a 10-week physical exercise intervention; for the 2014 data collection, participants with no regular exercise routine were recruited for a single-day measurement. After exclusion of participants with contaminated EEG data or lack of behavioural data or fitness assessment, the data of 41 young adults (age range 20–30 years; mean = 23.6; SD = 2.8) and 90 older adults (age range 63–81 years; mean = 68.1; SD = 4.4) were included for further analysis. Young and older adults were roughly similar in terms of educational background.

In **Study III**, a population-based sample of 708 participants (age range 18–88 years) was recruited by the Cambridge Centre for Ageing and Neuroscience in the UK (Cam-CAN). (For a detailed description of the study, see Shafto et al., 2014.) Of the initial 708 participants, 646 had valid MRI data for our purposes—that is, T1, T2 and DTI/DKI weighted MRI. Participants who did not complete the reaction time task (N = 75) were also excluded, as were participants with outlying FA values (more than 3 times the interquartile range above or below the age decile mean) (N = 25). In total, then, the remaining number of participants for **Study III** was 399 (age range 18–87 years; 221 females). The age distribution of the sample was approximately symmetric (skewness = .03; standard error of mean (SE) = .12).

All participants gave written informed consent. Ethical approval was obtained from the ethical committee of the University of Jyväskylä for **Study I**, from the ethical committee of the Central Finland Health Care District for **Study II** and from the Cambridgeshire 2 (now East of England—Cambridge Central) Research Ethics Committee for **Study III**. The experiments were undertaken in accordance with the Declaration of Helsinki.

2.2 Stimuli and procedure

In **Studies I** and **II**, participants were seated in a chair in an electrically shielded, dimly lit room to measure event-related potentials (ERPs) and were monitored by video camera. Participants were instructed to avoid all additional body movement, facial expressions, talking and excessive head movement, and were told not to pay any attention to any stimuli. In **Study I**, each participant's somatosensory responses were measured while they focused on a radio play via a loudspeaker placed about 50 cm above their head, with a volume subjectively comparable to a normal speaking voice. In **Study II**, somatosensory and auditory responses were measured while the participant watched a silent movie played on a screen at a distance of about 1.5 metres.

In **Studies I** and **II,** somatosensory stimulation was generated by means of a constant current stimulator (Digitimer Ltd, model DS7A, Welwyn Garden City, UK). Electrical pulses of 200 μs duration were delivered through flexible metal ring electrodes moistened with conductive jelly (Technomed Europe Ltd, Maastricht, Netherlands), attached to the left forefinger and the little finger, stimulating the anode above the distal phalanx and the cathode above the

proximal phalanx. A run of 1000 stimuli was delivered with a stimulus onset asynchrony (SOA) of 500 ms in **Study I** and a randomly varying SOA of 400, 450 or 500 ms in **Study II**. In an oddball condition, 'standard' stimuli were frequently presented at probabilities of 85% and 86%, and rare 'deviant' stimuli were presented at probabilities of 15% and 14% in **Study I** and **Study II**, respectively. For all participants, standard and deviant stimuli were applied to both forefinger and little finger, with counterbalanced ordering across participants (Figure 2).

In **Study II**, auditory stimuli were also presented in addition to somatosensory stimuli. Sinusoidal sounds (50 ms in duration with 10 ms onset and offset time) were played through a loudspeaker placed 90 cm above the participant's head, at an intensity of 75 dB SPL (sound pressure level). Both frequencies (1000 Hz or 750 Hz) were applied as standard or deviant stimuli in counterbalanced order across all participants. A run of 1000 stimuli were presented with varying SOA of 400-450-500 ms (i.e. SOA varied randomly between stimuli being either 400, 450 or 500 ms), of which 86% were standard stimuli and 14% were deviant stimuli.

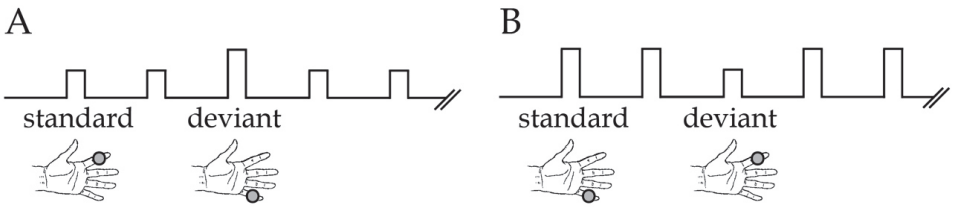

FIGURE 2 A schematic overview of the somatosensory oddball paradigm in Study I and II. For each participant both stimulus locations were applied as standard and deviant stimulus in a counterbalanced order between the participants. A. A stimulus condition where the frequently presented standard stimulus was an electric pulse to forefinger and the rare deviant stimulus an electric pulse to little finger. B. A stimulus condition where stimulation to little finger served as the standard stimulus and stimulation to index finger as a deviant stimulus.

2.3 Recording and preprocessing of EEG data in Studies I and II

In **Study I,** electroencephalography (EEG) signals were recorded at 30 scalp locations, using a Brain Vision Recorder software (Brain Products GmbH, Munich, Germany) amplified with Brain Vision QuickAmp and filtered online from 0.1 to 100 Hz, with a sampling rate of 1000 Hz. Linked left and right mastoid electrodes served as a reference for all Ag/AgCl electrodes on the electrode cap (Easy Cap QA40) according to the modified International 10–20 System (at FP1, FP2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, T7, T8, C3, C4,Cz, CP1, CP2, CP3, CP4, CP5, CP6, Pz, P3, P4, P7, P8, Oz, O1 and O2). The ground

electrode was placed in the middle of the forehead. Blinks and eye movements were measured by bipolar electrodes: one lateral to the right orbit and the other above the left eye.

In **Study II**, a high-impedance amplifier and a 128-channel EGI Sensor Net (Electrical Geodesics Inc., Hydrogel GSN 128, 1.0) were used to record EEG signals. The sampling rate was 1000 Hz, and data were filtered online with a band pass of 0.1–400 Hz. During recording, the vertex electrode (Cz) was used as reference, and the ground electrode was placed posterior to the vertex.

In **Studies I** and **II**, Brain Vision Analyzer 2.0 software (Brain Products GmbH) was used to analyse the data. Eye blinks were removed using the Gratton Coles method (Gratton, Coles, & Donchin, 1983), and channels with excessive noise and insufficient skin contact were interpolated using a spherical spline model. Offline, an average reference was applied, and electrode signals were filtered with a low cut-off of 0.1 Hz and a high cut-off of 20 Hz (with 24 dB/octave roll-off). In addition, a 50-Hz notch filter was applied. In the EEG data, excessively large amplitude values (more than ± 90 µV from peak to peak in **Study I** and ± 100 µV in **Study II**) were rejected, and low activity periods (< 0.5 µV of change within a 100 ms range) were removed.

In **Study I**, stimulus-locked time windows of 600 ms were extracted, from 100 ms prior to stimulus onset to 500 ms after stimulus onset. The segments were corrected with baseline mean amplitude between -100–0 ms. Visual inspection of the averaged and segmented EEG data revealed differences between standard and deviant responses for P50 (30–80 ms post-stimulus), N80 (40–110 ms post-stimulus), and MMR-like responses at 180–220 ms and 250–290 ms after stimulus onset. Maximum peak amplitude values were extracted from the C4 electrode site for P50 and N80 (Shinozaki et al., 1998). For the later responses, labelled as early and late MMR, mean amplitude values from nine electrode sites (FC1, Fz, FC2, C3, Cz, C4, P7, Pz, P8) were calculated following Retuccia et al. (2009).

In **Study II**, the data were segmented as stimulus-locked time windows of 600 ms (from 200 ms prior to stimulus onset to 400 ms after stimulus onset). The segments were corrected with a pre-stimulus onset baseline of 200 ms. Visual inspection of the grand-averaged data indicated potential group differences for somatosensory P50, N80, sMMR, sP3a, and auditory aN1, aMMN and aP2. The maximum peak amplitudes for P50 and N80 at C4 and latencies were extracted from time windows of 30–80 ms (P50) and 40–110 ms (N80) after stimulus onset. For later ERPs, the regions of interest (time windows and electrode sites) for each ERP component (sMMR, sP3a, aN1, aMMN, and aP2) were selected by permutation tests (Maris & Oostenveld, 2007); 4000 permutations were performed, starting with all 128 electrode sites and the 400 ms time window after stimulus onset, using BESA Statistics 1.0 software (BESA GmbH). As part of this process, average responses to standard and deviant stimuli were compared in the group of young adults as a reference for the older adult group. Time windows were defined by first identifying the time point with the highest *t*-value for each component and then using this time point as the centre of the

time window, yielding the following time windows: 153–193 ms after stimulus onset for sMMR; 258–358 ms for sP3a; 88–138 ms for aN1; 139–189 ms for aMMN; and 208–280 ms for aP2. The applicability of time windows based on the permutation tests was confirmed by visual observation of the grand-averaged differential responses (deviant minus standard responses). As in the case of time window selection, electrode sites were selected for analysis by first finding the electrode with the highest *t*-value in the middle of each selected time window and then defining the surrounding electrodes (4–5 for each). The activity of electrode sites within the region of interest was averaged. The definition of regions of interest was based on the young adult data, and the same electrode locations and time windows were used in the analysis of older participants' data, as there were no substantial differences between the groups.

2.4 Collecting and preprocessing of MRI DTI data in Study III

MRI data were collected using a Siemens 3T TIM TRIO (Siemens, Erlangen, Germany). To estimate white matter integrity, diffusion-weighted images (DWI) were acquired using a twice-refocused-spin-echo sequence, with 30 diffusion gradient directions each for b-values 1,000 and 2,000 s mm – 2, and three images acquired using a b-value of 0 (TE = 104 ms, TR = 9.1 s, voxel size = 2 × 2 × 2 mm3, field of view (FOV) = 192 × 192 mm2, 66 axial slices, GRAPPA acceleration factor = 2).

All pre-processing was completed using a combination of custom MATLAB scripts and functions from FSL version 4.1.8 (bet, eddy, dtifit, and TBSS). DWI data were pre-processed for eddy currents, and an affine registration model was used to correct for subject motion. After removal of non-brain tissue, a non-linear diffusion tensor model was fitted to the DWI volumes. Non-linear fitting of the diffusion tensor provides a more accurate noise modelling than standard linear model fitting and enables various constraints on the diffusion tensor, such as positive definiteness. The tensor's eigensystem was used to compute the fractional anisotropy (FA) at each voxel; FA maps were spatially normalized into a standard stereotactic space using tract-based spatial statistics (Peled, Friman, Jolesz, & Westin, 2006), with a JHU White Matter Atlas (http://cmrm.med.jhmi.edu/) as the target. Images were then smoothed with a 6 mm full width at half maximum Gaussian kernel to address possible residual errors and inter-individual variability, and to ensure that the normality requirements of parametric statistics were met. They were then masked with a binarised version of each participant's FA map; voxels below an FA threshold of 0.35 were not considered for further analysis.

Next, mean FA values over 21 bilaterally symmetrical tract ROIs from the JHU White Matter Atlas were extracted for subsequent analysis; these were genu of corpus callosum, body of corpus callosum, splenium of corpus callosum, column and body of fornix, fornix (cres), cerebral peduncle, anterior limb of internal capsule, posterior limb of internal capsule, retrolenticular part

of internal capsule, anterior corona radiata, superior corona radiata, posterior corona radiata, posterior thalamic radiation, sagittal stratum, external capsule, cingulate gyrus, hippocampus, superior longitudinal fasciculus, superior fronto-occipital fasciculus, uncinate fasciculus and tapetum.

2.5 Behavioural measures and questionnaire data

In **Study II**, participants' cognitive performance was assessed using a number of neuropsychological tests targeting domains that are known to be sensitive to ageing (Hedden & Gabrieli, 2004). Executive functions and working memory were tested using the Stroop Colour-Word Test (Lorenzo-López, Amenedo, Pazo-Alvarez, & Cadaveira, 2004), Trail Making Test A & B (Bowie & Harvey, 2006) and the Letter-Number Sequencing Task (Crowe, 2000). In the Stroop Colour-Word Test participant was handed a sheet with colour words printed in incongruent colours, and the task was to name the colour in which the word was written, prompting inhibition to read out loud the written word. Trail Making Test A assessed basic attention and psychomotor speed by participant's ability to connect 25 numbers in ascending order as fast as fast as possible yet avoiding errors on an A4-paper without lifting the pencil. In Trail Making Test B that requires divided attention, the paper included both numbers and letters. The participant was asked to connect numbers and letters by turns in ascending and alphabetical order.

Verbal memory performance was tested using the Logical Memory Task (Elwood, 1991) and the Digit Span Task (Ramsay & Reynolds, 1995), and nonverbal memory was assessed using the Visual Reproduction Task (Elwood, 1991). In the Logical Memory Task immediate and delayed auditory memory were assessed by telling the participant a short story that was then asked to be repeated immediately as accurately as possible. Hereupon the recall another story was told, which was followed by its immediate recall. In approximately an hour later the participant was asked to repeat the story anew. In the Digit Span Task, the participant was told a random sequence of numbers, which were asked to be repeated. If the recall was correct, the sequences eventually grew in length. Backward digit span task required the participant to repeat the told sequence in backward order, involving processing of the digits in the working memory. In Letter-Number Sequencing Task the participant was asked to repeat random series of letters and numbers reorganising the numbers in numerical order and then letters in alphabetical order.

In addition, psychomotor speed and voluntary motor control were assessed using the Finger Tapping Task (Ruff & Parker, 1993). In the task, the participant pressed a button on a mechanical tally counter with their thumb aiming to tap as many times as possible in 10 second span. The task was completed with the left hand three times consecutively, and then with the right hand. The scores for each hand were averaged across the three trials. All the cognitive tests were administered during a 60-minute session by a licensed

psychologist or a trained research assistant. The tests and their characteristics, along with supplementary data, are detailed in Table 5 of the original publication (Strömmer, Põldver, et al., 2017).

In **Study III,** participants' visuomotor reaction times were assessed using a simple response time task (Shafto et al., 2014), in which participants are asked to press as quickly as possible with their index finger when they see the index finger in an image of a hand turning black on the screen. To assess more general fluid intelligence, participants also completed the Cattell Culture Fair Test (Cattell & Cattell, 1960), which contains various nonverbal reasoning tasks with multiple choice responses.

In **Study II**, older adults' physical fitness was objectively measured using a six-minute walk test (Crapo et al., 2002) and total body fat percentage, based on a dual-energy X-ray absorptiometry (DXA) (Delphi QDR series, Hologic, Bedford, MA, USA). The six-minute walk test was conducted on a 200-metre indoor track, during which participants' heart rate was monitored at one-minute intervals. Body Mass Index (BMI) was calculated for both older and young adults. Self-reported physical activity among older adults was quantified on a five-point scale of medium-intensity activity (from 1 = less than 1 hour per week to 5 = more than 5 hours per week).

In **Study III**, information about physical activity was gathered as part of a larger self-completed questionnaire that asked about education, training, travel, hobbies, and social activities. To estimate an average for total typical daily activity during wake time, physical activity energy expenditure (PAEE, kJ/day/kg) was calculated for each individual by translating self-reported activities into metabolic equivalents (METs) (Ainsworth et al., 1993; Ainsworth et al., 2011), based on the standard definition of 1 MET as 3.5 ml O2 per min per kg (or 71 J per min per kg) for resting metabolic rate (Henry, 2005). Additionally, to investigate PAEE composition in terms of the nature of included activities, PAEE was divided into four subtypes: home and housework-related activity; voluntary leisure activity and exercise; work-related activity; activity related to commuting to work and other travel. The questions about physical activity were based on items from the European Prospective Investigation into Cancer Study-Norfolk Physical Activity Questionnaire (EPIC-EPAQ2) (Wareham et al., 2002). The full questionnaire can be found in the Supplementary Information section of the original publication of **Study III** (Strömmer, Davis, Henson, Tyler, & Campbell, submitted).

2.6 Statistical analyses

In **Studies I** and **II**, differences in response amplitudes between stimulus types and between the age groups for each brain response were tested using repeated measures multivariate analysis of variance (MANOVA). In **Study I**¸ laterality (left, medial, right) and anteriority (frontal, central, parietal) were used as within-subject factors to examine the scalp topography of differences between

stimulus types. In **Study II**, as the regions of interest were based on permutation analyses, only two-way MANOVAs were used. In addition, for the analysis of early latency somatosensory ERPs (P50 & N80) in **Study II,** stimulus intensities to forefinger and little finger were used as covariates in a univariate analysis of covariates (ANCOVA) because of the higher sensory thresholds and consequent higher stimulus intensities in the older group than in the young adults. Wherever group differences were found, differential responses (deviant minus standard responses) were calculated separately for older and young adults. Analysis of variance (ANOVA) were then performed in **Study I**, along with independent samples t-tests (two-tailed, bootstrap statistics with 1000 iterations) in **Study II**, to compare standard and deviant responses between the two groups. Effect size estimates were described as partial eta squared (η_P^2) scores for MANOVA and Cohen's d for t-tests.

To reduce the dimensionality of the cognitive test scores for further analysis, a principal component analysis (PCA) was performed in **Study II**. Following an exploratory analysis, an oblimin-rotated PCA with Kaiser Normalisation yielded four components, which were labelled *executive function*, *error susceptibility*, *explicit memory* and *working memory*. Factor loadings for the 14 included test scores are described in the supplementary data of the original publication of **Study II** (Strömmer, Põldver, et al., 2017).

In **Study I**, Pearson's correlation coefficients, controlled for age, were computed separately for young and older adults to investigate the relationship between stimulus intensity and differential ERPs. In **Study II,** one-tailed Pearson's correlation coefficients, controlled for age and education, were computed separately for both age groups to examine the relationships between differential ERPs and PC loadings from the cognitive test scores, and physical fitness measures. Bootstrap statistics were performed with 1000 iterations and CIs of 99% and 95%. The threshold for statistical significance was $p < .05$. In **Study III**, the relationship between age and total PAEE was examined by computing Pearson's correlation coefficients, partialling out gender and education. As the distributions of PAEE subtypes were skewed, Spearman's rank correlation coefficients (controlled for gender and education) were computed to examine age-related changes in the types of activity contributing to total PAEE.

In **Study III**, a series of mediation analyses was performed to investigate whether physical activity has an effect on age-related decline in white matter integrity. In the mediation analysis, the third mediator variable fully or partially accounts for the relationship between an independent predictor and dependent outcome variables (Baron & Kenny, 1986). In each analysis, the independent factor was age; the dependent factor was one mean FA within one of the 21 white matter tracts, and the mediator was level of physical activity (i.e. PAEE). In the second phase, we tested the relationship between white matter integrity for those tracks that showed a significant mediation effect and age-related slowing and fluid intelligence. To this end, we performed another set of mediation analyses, using age as the independent factor, with reaction time or

Cattell Culture Fair Test score as the dependent factor and mean FA within each of the previously identified tracts as the mediator. Direct effects of age on FA and reaction time/Cattell were also included in these regressions. In mediation analyses, statistical significance is typically indicated by significant attenuation of the relationship between predictor and outcome variables, denoted here by a 95% confidence interval for standardized regression coefficient that does not cross zero. All significance tests were two-tailed, and false discovery rate (FDR) (Benjamini & Hochberg, 1995) was applied at 0.05 to protect against familywise Type I error.

TABLE 1 Summary of methods

Study	Sample	Measures	Statistics
I	N = 31 18 young adults, age range 22–29 years, mean = 25, SD = 2.0, six females 13 older adults, age range 66–95 years, mean = 75, SD = 8.3, nine females Recruited in 2010-2011 in Finland	ERP (somatosensory stimuli)	ANOVA Repeated measures MANOVA Paired samples *t*-tests Pearson's correlation coefficient (*r*) Partial eta squared and Cohen's *d* for effect size estimates
II	N = 131 41 young adults, age range 20–30 years, mean = 23.6, SD = 2.8, all female 90 older adults, age range 63–81 years, mean = 68.1, SD = 4.4, all female Recruited in 2013-2014 in Finland	ERP (somatosensory and auditory stimuli) Cognitive tests (Stroop, WMS-R: logical memory & visual reproduction, digit span, letter- number sequencing, TMT A & B, finger tapping test) Body composition (DXA) Aerobic fitness (6-min walk test)	ANOVA ANCOVA Repeated measures MANOVA Paired samples *t*-test Permutation test PCA Pearson's *r* with bootstrap statistics and partial correlation Partial eta squared and Cohen's *d* FDR
III	N = 399 Population-based sample Age range 18–87 years, 221 females, skewness = .03, SE = .12 Recruited in 2010-2014 in the UK	MRI-DTI (white matter/FA) Fluid cognition (Cattell) Simple reaction times (RT) Physical activity (EPAQ/PAEE)	Mediation analysis Pearson's *r* and partial correlation Spearman's rank correlation coefficient and partial correlation FDR

3 SUMMARY OF RESULTS

The results of **Study I** showed that the sMMR for location changes is diminished in amplitude in older adults (n = 13, 66–95 years) as compared to young adults (n = 18, 22–27 years), confirming that the sMMR can reveal differences between the young and older adults in sensory-cognitive processes, as hypothesised. In **Study II** it was hypothesised that both sMMR and aMMN are diminished in amplitude in older (n = 90, 63–81 years) compared to young adults (n = 41, 20–30 years), and that these brain responses correlate with cognitive test scores. It was also assumed that better aerobic fitness is associated with better cognitive performance and less attenuated ERP amplitudes in older adults. The results of the **Study II** confirmed that task-irrelevant somatosensory and auditory ERP amplitudes are differentially linked to cognitive performance in young and older adults, and that physical fitness is associated with somatosensory ERPs and executive functions in older adults. In **Study III**, it was hypothesised that physical activity mediates age-related decline in white matter integrity, especially within those tracts most susceptible to age-related decline. In addition, it was hypothesised that white matter integrity mediates both age-related slowing of reaction times and age-related decline in fluid intelligence test scores. The results of the **Study III** showed that physical activity mitigates the effects of age on white matter integrity in four anterior white matter tracts, namely in the genu of the corpus callosum (GCC), the anterior limb of the internal capsule, the external capsule and the uncinate fasciculus. The results also demonstrated that white matter integrity in the GCC significantly mediated the effect of age on reaction time, but not on the fluid capabilities, against our hypothesis. Table 2 summarises the research questions, hypotheses and results.

TABLE 2 Summary of research questions, hypotheses and results of the original studies.

Study	Research questions	Hypotheses	Results
I	Does healthy ageing have an effect on somatosensory change detection?	Somatosensory mismatch response (sMMR) is diminished in amplitude in older as compared to young adults.	The hypothesis was supported; somatosensory change detection mechanism is altered in ageing.
II	Are auditory and somatosensory change detection mechanisms altered in ageing, and if so, is this associated with age-related decline in cognitive performance?	Both sMMR and aMMN are diminished in amplitude in older as compared to young adults, and these brain responses correlate with cognitive test scores.	The hypotheses were partly supported; task-irrelevant somatosensory ERP amplitudes are diminished in normal ageing and are linked to cognitive performance.
	Is better physical fitness associated with less altered brain responses and better cognitive performance in ageing?	Better aerobic fitness is associated with better cognitive performance and less attenuated ERP amplitudes in older adults.	Higher somatosensory response amplitudes are associated with better executive functions and better physical fitness in older adults.
III	Does physical activity mitigate age-related decline of white matter integrity?	Physical activity mediates age-related decline in white matter integrity, especially within those tracts most susceptible to age-related decline.	The hypotheses were partly supported; physical activity mitigates age-related degeneration of white matter microstructure within several frontal white matter tracts.
	Does white matter integrity in those tracts sensitive to physical activity mediate age-related decline in reaction times and fluid intelligence?	White matter integrity mediates both age-related slowing of reaction times and age-related decline in fluid intelligence test scores.	White matter integrity in those tracts sensitive to positive effects of physical activity mediates age-related slowing of reaction times but not age-related decrease in fluid intelligence.

3.1 Study I: somatosensory change detection declines with ageing

Study I examined whether normal ageing has an effect on somatosensory change detection mechanism by comparing brain responses to electrical pulses to different fingers in healthy young and older adults. The results showed that sMMR for stimulus location changes was attenuated in amplitude and

prolonged in latency in older as compared to young adults. More specifically, somatosensory stimulation of different fingers elicited differential responses to deviant and standard stimuli at two different latency ranges labelled early sMMR (at about 180–220 ms after stimulus onset) and late sMMR (at about 250–290 ms after stimulus onset). Early sMMR was found at central-medial electrode sites only within the young adult group. In contrast, late sMMR was attenuated in amplitude and more narrowed, with frontal scalp distribution, in older adults as compared to young adults, who showed wider frontal-central scalp distribution of late sMMR (Figure 3).

This study showed that sMMR for location changes is sensitive to ageing, serving as proof of concept for **Study II** and confirming that sMMR is a suitable tool for studying sensory-cognitive changes in ageing.

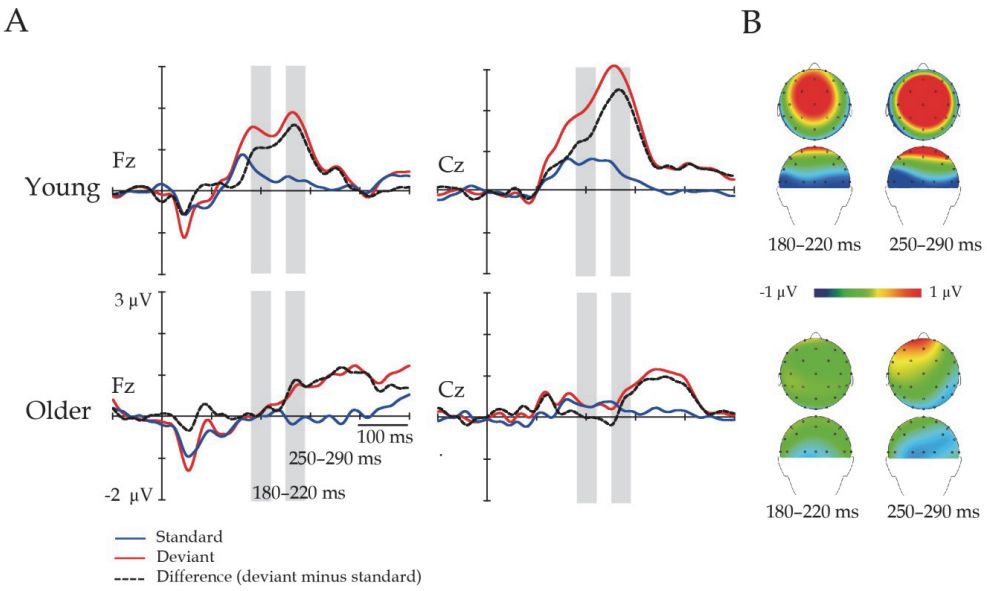

FIGURE 3 A. Grand-averaged brain responses to somatosensory stimuli in young and older adults in Study I. The grey area represents the latency range for early sMMR (180–220 ms) and for late sMMR (250–290 ms). B. Average scalp voltage maps of differential responses (deviant minus standard) for young and older adults at the latency ranges of early and late sMMR. (Figure modified from Strömmer et al., 2014).

3.2 Study II: higher brain response amplitudes are associated with better cognitive performance and better physical fitness

Study II examined whether age-related decline in the somatosensory and auditory change detection mechanisms is associated with age-related alterations in cognitive performance. We also tested whether better physical

fitness is associated with less altered brain responses and better cognitive performance in older adults. The results showed that sMMR (153–193 ms after stimulus onset) is diminished in amplitude in older as compared to young adults, partly replicating the finding from **Study I** (Figure 4). However, unlike **Study I**, the sMMR (i.e. early sMMR in **Study I**) was not absent in older adults in **Study II** but was statistically significant in that group (Figure 4). There were no differences between the age groups in the aMMN amplitude (Figure 5). aN1 and aP2 were, instead, increased in amplitude due to larger responses to standards in older as compared to young adults (Figure 5).

In older adults, higher sMMR amplitudes were associated with better executive functions, whereas in young adults, higher aMMN amplitudes are associated with better working memory performance. In addition, **Study II** showed that objectively measured aerobic fitness in older adults is linked to higher response amplitudes of somatosensory deviance detection-related ERPs and to better executive functions. The cognitive performance is here reported as composite scores (i.e. principal component) from several cognitive test scores that reflect performance in a common cognitive domain. Good executive functioning refers to good ability to inhibit automatic reactions in *Stroop Colour-Word Test* and well-functioning attention and psychomotor control in *Trail Making Test A and B*. As for working memory composite score, it is mainly comprised of sensory memory performance in the *Digit Span Task* and working memory performance in *Digit Span Backwards Task* and *Number-Letter Sequencing Task*.

Overall, the results of **Study II** confirmed that task-irrelevant somatosensory and auditory ERP amplitudes are differentially linked to cognitive performance in young and older adults. Additionally, physical fitness is associated with somatosensory ERPs and executive functions in older adults.

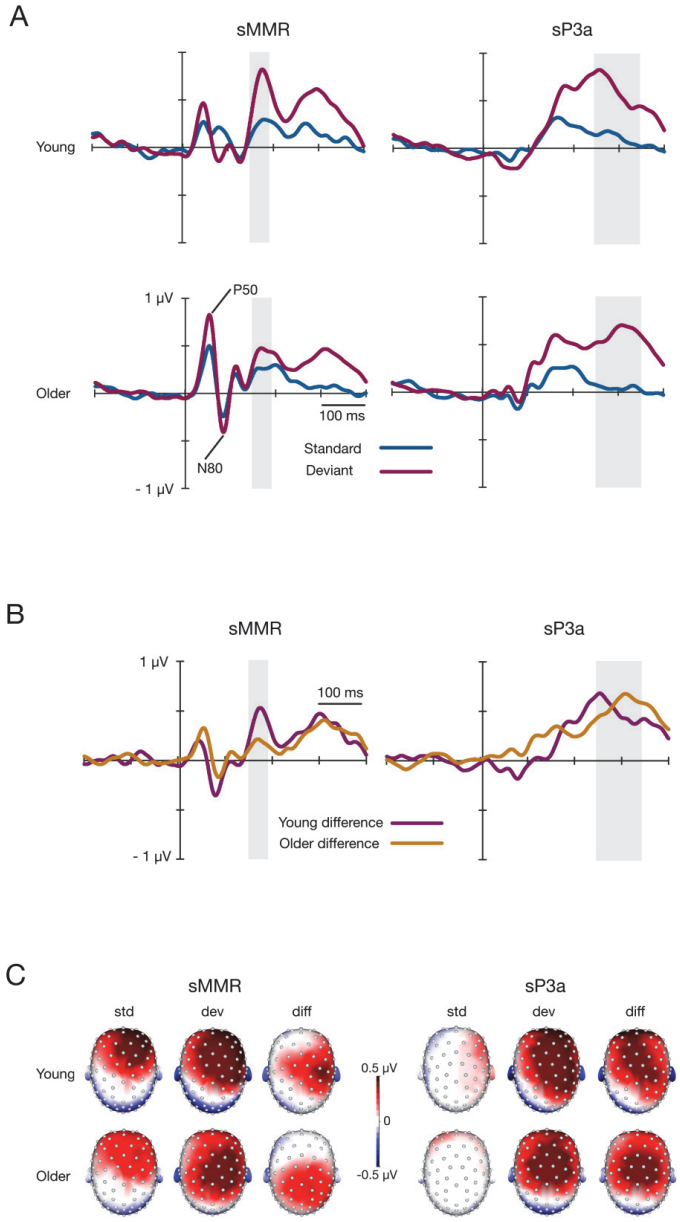

FIGURE 4 A. Grand-averaged brain responses to somatosensory standard and deviant stimuli in young and older adults in Study II. The grey area represents the latency range for sMMR (153–193 ms) and for sP3a (258–358 ms). B. Differential (standard minus deviant) waveforms from young and older adults. C. Average scalp voltage maps for young and older adults at the latency ranges of sMMR and sP3a. (Figure as originally published in Strömmer et al., 2017).

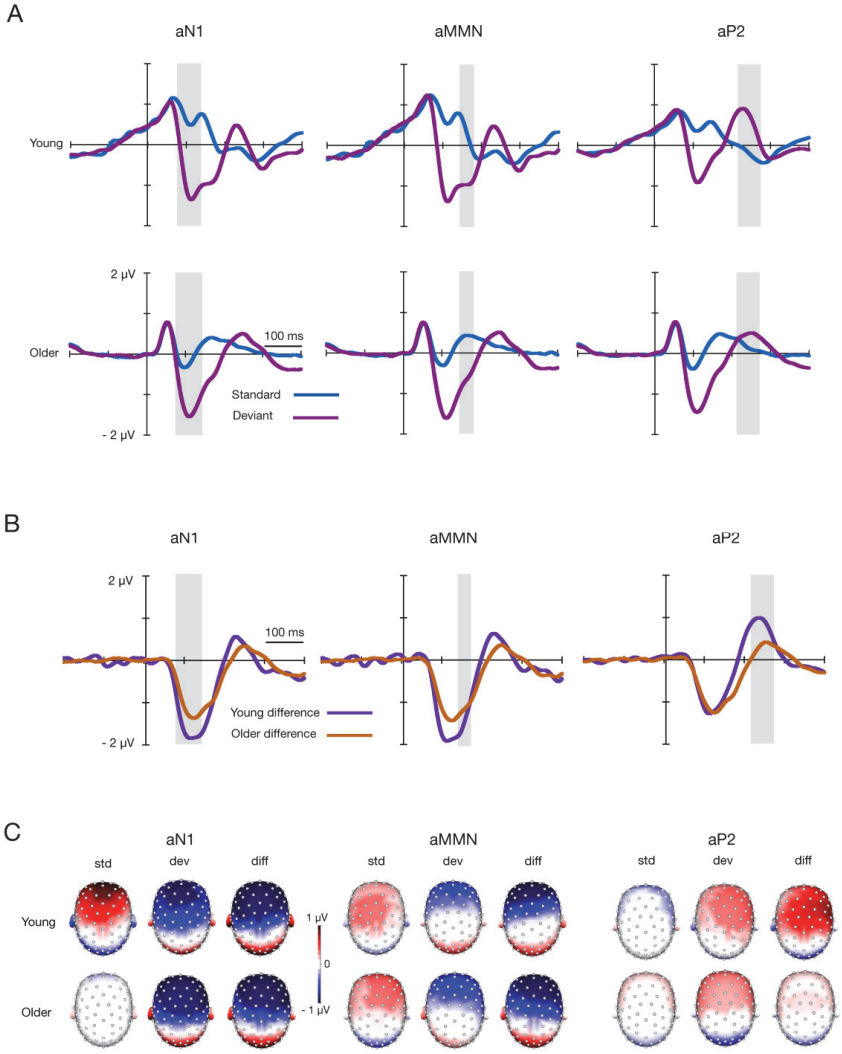

FIGURE 5 A. Grand-averaged brain responses to auditory standard and deviant stimuli in young and older adults in Study II. The grey area represents the latency range for aN1 (88–138 ms), aMMN (139–189 ms) and for aP2 (208–280 ms). B. Differential (deviant - standard) waveforms from young and older adults. C. Average scalp voltage maps for young and older adults at the latency ranges of aN1, aMMN and aP2. (Figure as originally published in Strömmer et al., 2017).

3.3 Study III: physical activity mitigates age-related white matter loss

Study III examined whether physical activity mediates the effect of age on white matter integrity. We also tested whether age-related slowing of reaction times and declines in fluid intelligence are mediated by white matter integrity within those tracts that benefit from physical activity. To answer these research questions, we also investigated the effect of age on physical activity, white matter integrity, reaction time and fluid intelligence within a healthy, population-based sample covering the adult lifespan.

The results showed that overall physical activity (i.e. total PAEE) gradually declines with increasing age, regardless of gender or educational background. By investigating different types of activity, we were also able to show that activities related to voluntary leisure time and hobbies, as well as chores and home-based activities, remain stable across the lifespan while work and commuting-related activity decline with increasing age, probably contributing to the decline in total daily energy expenditure.

We found that white matter integrity throughout the cerebrum declines with increasing age. That is, FA decreased with age in all of the analysed white matter tracts other than the posterior limb of internal capsule, where FA was found to increase with age. The degenerative effect of age on white matter integrity was relatively large in the genu and body of the corpus callosum, fornix, anterior corona radiata, posterior thalamic radiation, sagittal stratum and tapetum.

The mediation analyses showed that total PAEE mediates the age-FA relationship for four anterior white matter tracts; higher levels of physical activity mitigate age-related degeneration of white matter microstructure in the genu of the corpus callosum (GCC), the anterior limb of the internal capsule, the external capsule and the uncinate fasciculus (Figure 6).

The second set of mediation analyses tested the relationship between cognitive performance (i.e. reaction time and fluid intelligence) and white matter integrity in those tracts that benefit from physical activity. We found that mean FA in the GCC significantly mediated the effect of age on reaction time, suggesting that preservation of white matter in the GCC is associated with less age-related slowing (Figure 6). We also found an association between white matter integrity in the external capsule and fluid abilities, but most of the variation in age-related changes in fluid abilities was explained by educational background and gender.

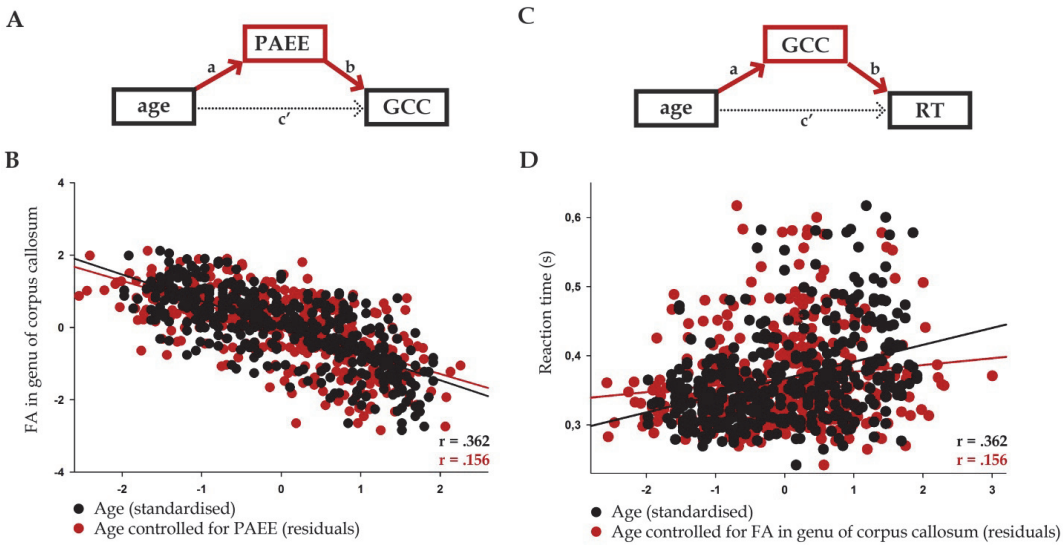

FIGURE 6 Schematic illustrations of mediation analyses and scatter plots of the main results of Study III. A. Mediation analysis to test whether physical activity mediates the effect of age on white matter integrity in the GCC. B. Relationship between white matter integrity (FA) and age (black dots, path c′ in figure A) and age controlled for PAEE (red dots, path ab in figure A) in the GCC. FA decreases gradually with age: r= -. 731, p < .001. The detrimental effect of age on FA is diminished when PAEE is partialled out from age: r= -. 688, p < .001. C. Mediation analysis to test whether white matter integrity in the GCC mediates the effect of age on reaction time. D. Relationship between reaction time and age (black dots, path c′ in figure C) and age controlled for FA in GCC (red dots, path ab in figure C). Reaction times become gradually slower with age: r = .362, p < .001. The effect of age on reaction time is diminished when FA in the GCC is partialled out from age: r = .156, p = .002. The results indicate that higher physical activity mitigates age-related differences in white matter integrity in the GCC, and white matter integrity in the GCC mitigates age-related differences in reaction time performance. (PAEE = physical activity energy expenditure (kJ/kg/day); FA = fractional anisotropy; GCC = FA in genu of corpus callosum; RT = reaction time).

In sum, the results of this dissertation showed that somatosensory brain responses that reflect brain's ability to detect changes in the sensory environment, and auditory brain responses that reflect encoding of the properties of perceived stimuli, alter with ageing. Higher amplitudes of the somatosensory change detection ERPs were associated with better executive functions in older adults. In addition, higher physical fitness was associated with better executive functions and higher ERP amplitudes in older adults. The results of this dissertation also demonstrated that physical activity mitigates the age-related degeneration of white matter integrity in several frontal tracts, in which, the white matter integrity mediates the age-related slowing of cognitive processing speed.

4 DISCUSSION

This dissertation investigated normal age-related changes in cortical sensory processing and cognitive functioning, and the role of physical fitness and physically active lifestyle on brain ageing and cognition. In **Study I**, the effect of age on the somatosensory change detection mechanism was studied by measuring ERPs for electrical stimulation of fingers in young and older adults. The sMMR amplitude was found to be diminished in older as compared to young adults, indicating that the somatosensory change detection mechanism is altered in ageing. These results served as proof of concept for **Study II**, which investigated whether age-related changes in the somatosensory and auditory change detection mechanisms are associated with age-related alterations in cognitive performance.

We also tested whether better physical fitness is associated with less altered brain responses and better cognitive performance in older adults. The results confirmed that somatosensory ERP amplitudes relate to change detection that auditory ERP amplitudes related to stimulus encoding diminish in ageing and that in older adults, higher somatosensory ERP amplitudes are linked to better executive functions and better objectively measured physical fitness. In **Study III**, the supposed preservative effects of a physically active lifestyle on the brain's white matter microstructure and cognitive performance were studied within a large population-based sample of healthy adults covering the life span. The results showed that higher daily physical activity mitigates age-related decline in white matter integrity in the GCC and in several frontal association tracts. Additionally, white matter integrity in the GCC was shown to mediate age-related slowing of cognitive processing speed, indicating an indirect relationship between a physically active lifestyle, white matter health and fundamental processing speed during ageing.

4.1 Cortical sensory processing alters with ageing

Study I found that sMMR to electrical pulses produced positive polarity deflections in the differential (deviant minus standard stimulus response) waveform at two consecutive latency ranges, labelled as early sMMR (180–220 ms after stimulus onset) and late sMMR (250–290 ms after stimulus onset). These results largely align with prior findings that sMMR exhibits either a negative or positive component (possibly depending on the direction of the generating dipole) at about 100–200 ms after the stimulus onset (Akatsuka et al., 2005; Kekoni et al., 1997; Shinozaki et al., 1998). In addition, a few studies have identified a subsequent component at about 180–250 ms in healthy adults (Spackman et al., 2007) and in children (Restuccia et al., 2009).

In **Study I**, both early and late sMMR were elicited in young adults; in older adults, early sMMR was absent, and late sMMR was diminished in amplitude as compared to young adults. In **Study II**, sMMR was also observed to shift towards positive polarity at 153–193 ms after stimulus onset in both age groups but diminished in amplitude in older adults. These results strengthen the findings of **Study I,** using a larger sample and a more objective method (i.e. permutation tests) of selecting the latency ranges and scalp topographies for each ERP component. In **Study II**, the response at the later latency was observed to conform to sP3a (258–358 ms after stimulus onset). While there was no difference in amplitude between the age groups, it is notable that the response latency of sP3a seems to be delayed in older adults as compared to young adults. However, the data did not allow investigation of the sP3a latency difference between the groups, as there was no clear sP3a peak for each individual. For that reason, mean amplitude values were applied in the analysis. The considerable overlap between response latencies of sP3a in **Study II** and late sMMR in **Study I** suggests that both represent sP3a (Naeije et al., 2016; Shen, Smyk, Meltzoff, & Marshall, 2017), although there is evidence of the bipartite nature of these sensory discrimination responses specifically for the somatosensory modality (Butler et al., 2011; Spackman et al., 2007). With attenuated sMMR but no changes in sP3 amplitude, this pattern of results suggests that the change detection mechanism is less well preserved than the subsequent automatic shift of attention in ageing.

In addition, we found that somatosensory P50 and N80 amplitudes were larger in older adults as compared to young adults in **Study II**. However, this was partly explained by higher sensory thresholds and associated higher stimulus intensities in older participants, which hampers the interpretation of the results. In **Study I**, somatosensory N80 latency was more prolonged in older than in young adults. These results are not directly comparable to previous findings from studies using a paired-pulse condition, but it is possible that age-related delay in N80 latency reflects an ageing-related decline in cortical gating of sensory input (Chao & Knight, 1997; Cheng & Lin, 2013; David-Jürgens &

Dinse, 2010) due to reduced inhibitory function (Bolton & Staines, 2012; Cheng & Lin, 2013; Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Lenz et al., 2012).

Contrary to our hypothesis and to earlier findings (Alain & Woods, 1999; Cooper et al., 2006; Gaeta, Friedman, Ritter, & Hunt, 2002), no age-related attenuation of aMMN was found in **Study II**, probably because of the use of a short inter-stimulus interval (Pekkonen et al., 1996; Pekkonen, Jousmäki, Partanen, & Karhu, 1993). As the MMN reflects a change detection involving comparison of a transient memory trace formed by repetitive standard stimuli and deviant sensory input, prolongation of the inter-stimulus interval makes this comparison process more demanding for the brain (Näätänen et al., 2012). However, age-related deterioration in the ability to form memory traces may not be manifested with short inter-stimulus intervals. In **Study II**, the inter-stimulus interval was relatively short (400–500 ms), which may explain why we found no group differences in aMMN.

Notably, in **Study II**, where the inter-stimulus interval was the same for both sensory modalities, somatosensory change detection as indexed by the mismatch response declined in older adults, but there was no evidence of any such effect in the auditory modality, suggesting that sMMR might be more sensitive to normal ageing than its auditory counterpart. However, in the auditory modality, age-related alterations were observed in the response amplitudes of N1 and P2, which are associated with stimulus encoding. The observed increase in response amplitudes for these ERP components in older as compared to young adults indicates alterations in cortical suppression of stimulus response in older adults.

The age-related changes in change detection and stimulus encoding demonstrated in **Studies I** and **II** might be explained by disturbed predictive coding of sensory information (Friston, 2005; Moran, Symmonds, Dolan, & Friston, 2014; Wacongne et al., 2012). As the predictive coding model presumes that the brain continuously updates an internal model of environment by synaptic plasticity in order to predict the causes of sensory input, the attenuation of brain plasticity with ageing is selective and specific to short-term sensory learning (Friston, 2005; Moran et al., 2014). In the somatosensory modality, then, age-related decline in change detection may be due to attenuated synaptic plasticity in the secondary somatosensory cortex, manifested as attenuated sMMR in older adults as compared to young adults (Naeije et al., 2018).

4.2 Brain responses are associated with cognitive performance and physical fitness in older adults

Study II showed that somatosensory ERPs, cognitive performance and objectively measured physical fitness were linked in older adults. Specifically, higher sMMR amplitude was related to better executive functions, as indexed

by a composite score of several cognitive test scores. In young adults, a similar association was found between aMMN amplitude and working memory capacity, suggesting that age-related changes and their contribution to changes in behaviour may be divergent for the two sensory modalities. In fact, rather than a generalised decline affecting all the inhibitory modalities equally, the ERP data suggest that the effects of normal ageing on cortical inhibitory mechanisms differ for motor and sensory modalities (Anguera & Gazzaley, 2012). Similarly, the findings of **Study II** suggest that the somatosensory change detection mechanism may be more sensitive to the effects of ageing than its auditory counterpart, at least in relation to frequency discrimination with a short inter-stimulus interval. Moreover, decline in working memory functions may precede alterations to auditory sensory memory in ageing while well-functioning auditory sensory memory may help to maintain working memory.

Various factors may influence decline in working memory. It has been shown that hard of hearing within older adults may contribute on ageing-related decline in memory tasks that depend on hearing (Lu, Daneman, & Schneider, 2016), and that cochlear-implants, primarily implanted to enhance hearing, also improve verbal cognition within older adults (Finke, Büchner, Ruigendijk, Meyer, & Sandmann, 2016). In **Study II**, however, the participants were healthy and their hearing was tested to be well above the auditory stimulus intensities. Previous studies have shown that verbal memory and executive functions, including conditional inhibition as in our study, predicts variance in aMMN amplitude for differences in inter-stimulus intervals in healthy older adults (Foster et al., 2013; Kisley et al., 2005). In our study, however, aMMN for frequency deviations was not associated with cognitive performance in older adults, probably because of the non-optimal inter-stimulus interval for revealing possible ageing-related alterations in sensory memory.

In **Study II,** longer distance in a six-minute walk test was associated with higher sP3a amplitude and better executive functions in older adults. These results suggest that being physically fit may help to preserve efficient cognitive functioning in late adulthood, especially in the domains of cognition that are susceptible to changes in ageing. This supports earlier prospective studies that found engagement in aerobic exercise to be beneficial to cognitive functioning in general, and to executive functioning in particular, in older adults (Colcombe & Kramer, 2003). Notably, in **Study II** better walk test performance was related to lower body mass index, lower body fat percentage and higher self-reported physical activity, suggesting that the six-minute walk test is a suitable measure of physical fitness in older populations (Du, Newton, Salamonson, Carrieri-Kohlman, & Davidson, 2009). To date, relatively few studies have examined the links between the brain's electrophysiological responses, cognitive performance and physical fitness. However, it has been shown that physically inactive older adults tend to have more problems in attentional control during demanding cognitive tasks, accompanied by smaller auditory P3a amplitudes than for more active control, which suggests that a physically active lifestyle may help to

protect against decreased inhibition of irrelevant stimulus features (Getzmann et al., 2013). Similarly, higher physical activity levels have been linked to faster cognitive processing and higher auditory N1 and P3b amplitudes (Chang et al., 2013). In addition, a recent twin study with young adults using an experiment similar to that in **Study II** showed that sMMR is a sensitive indicator of long-term physical activity (Tarkka et al., 2016).

4.3 Physical activity mitigates age-related decline in white matter integrity

In **Study III**, higher levels of daily activities were shown to be associated with better preserved white matter in ageing. Although the cross-sectional sample does not support causal inference, the results suggest that older individuals who are more active in their day-to-day lives exhibit more youth-like patterns of white matter microstructure in several adjacent anterior white matter tracts. Additionally, overall physical activity declined with increasing age and, in line with longitudinal diffusion tensor imaging analyses of healthy adults (de Groot et al., 2016; Raz et al., 2005), white matter integrity in our population-based sample of healthy adults decreased throughout the brain with increasing age.

Consistent with our findings, previous studies have shown that higher self-reported physical activity is associated with higher white matter volume (Benedict et al., 2013) and less age-related white matter atrophy (Gow, Bastin, et al., 2012) in older populations. Furthermore, higher objectively measured cardiorespiratory fitness and lifelong engagement in exercise are known to be associated with better white matter health in older adults, both in the cingulum (Marks et al., 2011; Tseng et al., 2013) and especially in the GCC (Johnson et al., 2012). These studies suggest that although the intensity of activity may affect the degree of benefit, any increase in physical activity is likely to have positive effects on white matter health in older adulthood. The white matter tracts between the prefrontal regions and medial temporal lobe are known to be particularly sensitive to variation in cardiorespiratory fitness (Oberlin et al., 2015). In agreement with **Study III**, recent evidence indicates that white matter integrity in certain tracts that are most susceptible to age-related atrophy (including the GCC but not all susceptible tracts) are specifically responsive to cardiorespiratory fitness (Hayes, Salat, Forman, Sperling, & Verfaellie, 2015).

In **Study III**, age-related decline in total physical activity energy expenditure was largely a consequence of reduced work and commuting-related activity in older adults while other sub-classes of activity (e.g. home and leisure-related activity) remained relatively stable across all ages from 18 to 87 years. In other words, activities of different kinds tend to affect total energy expenditure in different stages of life. While an active lifestyle involving outdoor play or travel is an important contributor to total energy expenditure in

childhood, life events influence most physical activity behaviours in adulthood (Condello et al., 2017).

A physically active lifestyle over longer periods of time not only protects brain structure in ageing but also aids general cognitive performance (Best et al., 2017). Importantly, increasing physical activity by following a walking programme has been shown to increase cardiovascular fitness, inducing increased white matter integrity in frontal and temporal regions and improvement in short-term memory (Voss et al., 2013). In **Study III**, age-related slowing of cognitive processing speed—a well-known phenomenon in cognitive ageing (Salthouse, 2000; 1996)—was mediated by white matter integrity in the GCC but not by white matter integrity in the other tracts associated with physical activity. Additionally, physical activity-related white matter tracts had only an approximate mediation effect on age-related changes in fluid capabilities, possibly because fluid intelligence has been linked to more anterior tracts (Kievit et al., 2016). Earlier findings have similarly suggested that age-related slowing of reaction times is related to white matter deterioration in the anterior parts of the corpus callosum (Salami et al., 2012), the anterior limb of the internal capsule (Madden et al., 2004) and more global white matter structure (Johnson, Diaz, & Madden, 2014; Kievit et al., 2016). It is possible that the associations found in **Study II** between physical fitness, brain responses and executive functions in older adults similarly reflect an indirect pattern of relationship between cardiorespiratory fitness and cognitive performance, mediated by structural connectivity in the brain.

4.4 Limitations of the methods

It must be acknowledged that there are some limitations in the methods used here that can be addressed in future studies. In **Study I**, the sample size was relatively small, and we did not control for gender and physical activity, which hampered comparison of results from **Studies I** and **II**. It is likely that participants in **Study I** were physically less active than those in **Study II**, half of whom were recruited for a physical exercise intervention study and may therefore have been more active than their age controls. Obviously, as all of the participants in **Study II** were female, these findings apply only to females.

In addition, the wide age range (66–95 years) of the older adults in **Study I** may hamper the interpretation of the results, since it is well known that brain structure and brain function face considerable changes within 30 years of late adulthood. However, in **Study II** where in an additional analysis conducted after the publication of the original report the group of older adults was divided into two groups, 63–70-year-old and 71–87-year-old adults, no differences in brain responses between the age groups were found.

Partialling out stimulus intensities and hearing thresholds from the brain response analyses confirmed that most of the findings are not explained by differences in peripheral sensory systems. The auditory stimuli in **Study II** were

not individually adjusted while the somatosensory stimuli were, so preventing direct comparison of change detection mechanisms in the two sensory modalities. However, ERPs were measured for frequency and location changes rather than for changes in stimulus intensity, and as the fixed intensity of sounds (75 dB) was well above the hearing threshold, this limitation may not be critical for interpretation of the results.

The cross-sectional sample in **Study III** meant that it was not possible to infer causal relationships between age, physical activity, white matter integrity and cognitive performance. It is obvious, however, that age (an independent factor in both of the mediation models) cannot be changed by the influence of other factors. We also assumed that cognitive processing speed is a result of nervous system functioning (i.e. white matter integrity) rather than the other way round (Gow, Corley, et al., 2012). However, any causal interaction between lifestyle factors (such as physical activity) and brain structure remains unresolved by **Study III**. It is clear that environment and behaviour can induce brain plasticity; at the same time, structural and functional changes in the brain clearly influence behaviour (e.g. willingness to engage in physical activity).

4.5 Conclusions and impact of the research

The present findings align with theories of cognitive ageing. First, the age-related decline in change detection mechanisms identified here is probably linked to hypothesised deteriorations in sensory memory, leading to decline in the brain's ability to predict sensory inputs from the environment (Friston, 2005; Moran et al., 2014). Age-related changes in this fundamental cognitive capability may further affect higher cognitive functions. Second, the present findings demonstrate that cognitive processing speed and executive functions (which are highly dependent on efficient and rapid processing) are linked to the brain's structural connectivity and cortical functions. Indeed, it has been proposed that age-related slowing of cognitive processing speed is crucial to general cognitive changes in ageing (Salthouse, 2000; Salthouse, 1996). In that regard, the present findings enhance understanding of the relationship between neural and behavioural changes in age-related cognitive performance changes. Third, the present research confirms that physical activity and aerobic fitness are beneficial to brain white matter, cortical sensory processing and cognitive abilities that are susceptible to decline with ageing. The evidence from a rapidly growing literature suggests that synaptic plasticity induced by exercise and physical activity is essential to the brain's capability to compensate for age-related neural atrophy and to maintain cognitive functioning (Reuter-Lorenz & Park, 2010).

Finally, Raichlen and Alexander's recently introduced adaptive capacity model (2017) provides a broader framework for further explication of the interactions between physical activity, ageing, brain changes and cognition, the key ensemble addressed in this dissertation. They propose that the reliance on a

physically active lifestyle for health maintenance is a legacy of our physically active evolutionary past. With respect to the energy-minimising principle, they note that the human brain, which accounts for a fifth of the body's total energy costs, is particularly susceptible to capacity reductions associated with reduced exercise-related metabolism (Raichlen & Alexander, 2017). On the same principle, age-related neural atrophy may be a response to the lesser energy demands of reduced physical activity, which may be mitigated or prevented by maintaining sufficient levels of physical activity, particularly when coupled with cognitive challenges (Raichlen & Alexander, 2017).

While the present findings apply to healthy populations, they also provide an important perspective for better understanding the vacillating boundary between normal age-related cognitive changes and prodromal symptoms of brain pathologies. For example, change detection-related brain responses are known to decline in cases of mild cognitive impairment and neurodegenerative diseases (for reviews, see Näätänen et al., 2012; Näätänen et al., 2011) and in patients with cerebellar lesions (Restuccia, Marca, Valeriani, Leggio, & Molinari, 2007). It follows that a fuller understanding of brain responses may help to distinguish prodromal symptoms of disease from normal age-related cognitive changes before these become evident in behaviour and daily functions that may be more easily maintained by compensatory functions. Importantly, the positive effects of physical activity on brain and cognition in normal ageing identified here may also help to prevent some degenerative brain diseases. In particular, there is already strong evidence that physical activity is inversely associated with risk of Alzheimer's disease, Parkinson's disease and other dementias (Hamer & Chida, 2009).

In the present research, the reduction in work-related activity (the main contributor to total daily energy expenditure in adulthood) at around 60 years of age is concurrent with the mean retirement age of our sample. It may be that people whose day-to-day activity level is highly dependent on work-related activities exhibit the greatest reduction in total activity in older age as compared to those who have an active lifestyle beyond their working life. That being so, it seems important to promote physical leisure activities among the retired elderly, possibly with the help of societal actions. Indeed, identifying efficient ways of maintaining healthy cognitive and physical functioning in older age is an emergent concern for society, as it has been estimated that by 2050, the number of people aged 60 or over will have doubled since 2015, and the number aged 80 or over will have tripled (He et al., 2016; United Nations, 2015).

In conclusion, this dissertation demonstrates that ageing alters cortical responses that reflect the brain's fundamental capability to encode properties of perceived stimuli and to detect changes in those stimuli. In older adults, these responses are associated with cognitive performance and physical fitness. It was also confirmed that a physically active lifestyle protects against age-related white matter atrophy and loss of cognitive processing speed. These findings support public health recommendations in relation to the benefits of a physically active lifestyle throughout the life span and into older age.

YHTEENVETO (FINNISH SUMMARY)

Ikääntyvät aivot, kognitiiviset toiminnot ja fyysinen aktiivisuus

Ikääntyessä aivoissa tapahtuu rakenteellisia muutoksia ja kyky käsitellä aisti-informaatiota muuttuu. Normaalin ikääntymisen myötä aivojen harmaa aine surkastuu ja valkea aine muuttuu hauraammaksi. Nämä muutokset aiheuttavat hermoverkkojen uudelleenjärjestymistä ja muutoksia aivojen aktiivisuudessa, mikä puolestaan johtaa muutoksiin tiedonkäsittelytoiminnoissa käyttäytymisen tasolla. Toisaalta käyttäytymisellä, kuten fyysisesti aktiivisella elämäntavalla, voi olla aivoja suojaavia ja toimintaa ylläpitäviä vaikutuksia myös ikääntyessä.

Ensimmäisessä osatutkimuksessa selvitin ikääntymisen vaikutuksia aivojen kykyyn havaita muutoksia aistiympäristössä mittaamalla aivovasteita eri sormiin annettuihin sähköisiin tuntoärsykkeisiin terveillä nuorilla ja ikääntyneillä aikuisilla. Aikaisemmissa tutkimuksissa on havaittu, että aivojen kyky havaita muutoksia äänissä heikkenee sekä normaalissa ikääntymisessä että rappeuttavissa muistisairauksissa. Tässä tutkimuksessa sähköiset tuntoärsykkeet saivat aikaan muutoksenhavaitsemiseen ja tarkkaavuuden suuntaamiseen liittyvää herätevastetta nuorilla. Ikääntyneillä muutoksenhavaitsemisvastetta ei havaittu lainkaan kun taas tarkkaavuuden suuntaamiseen liittyvä vaste oli voimakkuudeltaan heikentynyt nuoriin verrattuna. Tutkimuksessa osoitettiin ensimmäistä kertaa, että muutoksenhavaitsemista tuntoaistijärjestelmässä heijastavat aivovasteet ovat alttiita ikääntymiseen liittyville muutoksille.

Toisessa osatutkimuksessa tutkin kuulo- ja tuntojärjestelmän muutoksen havaitsemiseen liittyvien aivovasteiden ja kognitiivisten kykyjen yhteyttä nuorilla ja ikääntyneillä naisilla. Lisäksi selvitin fyysisen kunnon yhteyttä aivovasteisiin ja kognitiiviseen suoriutumiseen ikääntyneillä. Aikaisemmat tutkimustulokset osoittavat, että muutoksenhavaitsemiseen sekä ärsykkeen piirteiden luokitteluun liittyvät kuuloherätevasteet heikkenevät voimakkuudeltaan ikääntyessä. Nämä herätevasteet ovat ikääntyneillä yhteydessä kognitiiviseen suoriutumiseen. Tämän tutkimuksen tulokset osoittivat, että muutoksenhavaitsemisvaste tuntoaistijärjestelmässä oli voimakkuudeltaan heikentynyt ikääntyneillä nuoriin verrattuna. Kuuloaistijärjestelmässä sen sijaan ärsykkeen piirteiden tunnistamiseen liittyvät aivovasteet olivat heikentyneitä ikääntyneillä, mutta muutoksenhavaitsemisvasteessa ei havaittu eroa nuorten ja ikääntyneiden välillä. Lisäksi havaittiin, että ikääntyneillä voimakkaampi muutoksenhavaitsemisvaste tuntoaistijärjestelmässä on yhteydessä parempaan suoriutumiseen toiminnanohjausta vaativissa tehtävissä. Nuorilla puolestaan voimakkaampi kuuloaistijärjestelmän muutoksenhavaitsemisvaste oli yhteydessä parempaan suoriutumiseen työmuistitehtävissä. Hyvä aerobinen kunto oli ikääntyneillä yhteydessä hyvään toiminnanohjauskykyyn sekä suurempiin tuntoaistijärjestelmän herätevasteisiin.

Kolmannessa osatutkimuksessa selvitin fyysisen aktiivisuuden vaikutusta aivojen valkean aineen tiheyteen koko aikuisiän kattavassa populaatiota edustavassa otoksessa. Aiemmissa tutkimuksissa on osoitettu, että korkeampi fyysinen

aktiivisuus on vähäisempään ikääntymiseen liittyvään valkean aineen rappeutumiseen. Tässä tutkimuksessa selvitin, voiko fyysinen aktiivisuus jarruttaa ikääntymisen aiheuttamaa rappeutumista aivojen valkeassa aineessa, ja voiko valkean aineen suurempi tiheys fyysisestä aktiivisuudesta hyötyvillä aivoalueilla jarruttaa ikääntymiseen liittyvää kognitiivista heikkenemistä. Tutkimus osoitti, että fyysinen aktiivisuus laskee iän kasvaessa, erityisesti eläkeiän kynnyksellä, valkea aine rapistuu iän kasvaessa kauttaaltaan aivoissa ja tiedonkäsittelyn nopeus hidastuu tasaisesti kasvavan iän myötä. Tutkimus osoitti, että fyysinen aktiivisuus jarruttaa ikääntymiseen liittyvää valkean aineen rappeutumista usealla aivojen etuosan alueella. Lisäksi havaittiin, että eheämpi valkea aine aivokurkiaisen etuosassa, missä myös fyysisen aktiivisuuden vaikutukset ovat voimakkaita, on yhteydessä pienempään ikääntymiseen liittyvään tiedonkäsittelyn hidastumiseen.

Kaiken kaikkiaan tämän väitöskirjan tulokset osoittavat, että aivojen perustavanlaatuinen kyky havaita poikkeavuuksia aistiympäristössä sekä luokitella havaitun aistiärsykkeen ominaisuuksia heikkenee ikääntyessä. Nämä aivojen sähköisissä herätevasteissa näkyvät muutokset ovat yhteydessä tiedonkäsittelytoimintoihin sekä fyysiseen kuntoon ikääntyneillä. Lisäksi väitöskirja osoittaa, että fyysinen aktiivisuus ja hyvä fyysinen kunto voivat jarruttaa ikääntymiseen liittyvää aivojen rappeutumista ja aivotoiminnan muutoksia sekä suojata kognitiiviselta hidastumiselta. Tämän väitöskirjan tulokset antavat tukea kansanterveydellisille suosituksille siitä, että fyysisesti aktiivinen elämäntapa on hyödyllistä aivojen terveydelle sekä kognitiiviselle toimintakyvylle.

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ORIGINAL PAPERS

I

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Somatosensory mismatch response in young and elderly adults

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Aging is associated with cognitive decline and alterations in early perceptual processes. Studies in the auditory and visual sensory modalities have shown that the mismatch negativity [or the mismatch response (MMR)], an event-related potential (ERP) elicited by a deviant stimulus in a background of homogenous events, diminishes with aging and cognitive decline. However, the effects of aging on the somatosensory MMR (sMMR) are not known. In the current study, we recorded ERPs to electrical pulses to different fingers of the left hand in a passive oddball experiment in young (22–36 years) and elderly (66–95 years) adults engaged in a visual task. The MMR was found to deviants as compared to standards at two latency ranges: 180–220 ms and 250–290 ms post-stimulus onset. At 180–220 ms, within the young, the MMR was found at medial electrode sites, whereas aged did not show any amplitude difference between the stimulus types at the same latency range. At 250–290 ms, the MMR was evident with attenuated amplitude and narrowed scalp distribution among aged (Fz) compared to young (fronto-centrally and lateral parietal sites). Hence, the results reveal that the somatosensory change detection mechanism is altered in aging. The sMMR can be used as a reliable measure of age-related changes in sensory-cognitive functions.

Keywords: aging, event-related potential, mismatch negativity, oddball condition, somatosensory

INTRODUCTION

It is suggested that the brain can rapidly and effortlessly learn the regularities in the stimulus environment and predict what should happen in the future (Wacongne et al., 2012). The brain is capable to detect sudden changes in the perceptual environment even without attentive resources. In aging, the change detection and predictive coding of the environmental events is gradually declined (Ruzzoli et al., 2012; see also Winkler and Czigler, 2012). There is a growing concern to understand widely the aspects of healthy aging as the world's age breakdown is rapidly reversing; it is expected that in 2050 the world's population at ages over 65 years will be 2.5 times that of the population at ages 0–4 years, the opposite ratio to 1950 (Haub, 2011).

On neurophysiological approach on aging, event-related potentials (ERPs) provide important indicators for pre-attentive sensory processing. The mismatch negativity (MMN) is a component of ERPs that occurs when the brain detects a change in a background of homogenous events (Näätänen, 1992). Further, its elicitation reflects predictive coding of the stimulus environment (Garrido et al., 2009; Wacongne et al., 2012). The MMN has been originally discovered in the auditory modality (Näätänen et al., 1978), but there is extensive evidence of the existence of its visual analog (for reviews see Kimura, 2012; Winkler and Czigler, 2012).

In normal aging, the MMN amplitude in the auditory (Cooper et al., 2006; Schiff et al., 2008; Kiang et al., 2009; Näätänen et al., 2012; Cheng et al., 2013) and visual (Tales et al., 2002; Lorenzo-Lopez et al., 2004) modalities have been shown to decrease gradually. In addition, the latency of the auditory MMN seems to prolong with age (e.g., Gaeta et al., 2001; Bertoli et al., 2002). These changes in MMN have been argued to indicate the shortening of the sensory memory duration and deficits in the encoding of the information due to age-related decline of the functional integrity of the central sensory processing (Pekkonen, 2000; Cooper et al., 2006). Importantly, the attenuation of MMN has been shown to reflect the deterioration in cognitive functions (Kisley et al., 2005; Foster et al., 2013). In these studies, decrease in the MMN to changes in intervals between the sounds correlated with poorer performance in cognitive tasks requiring executive function.

The reports of the somatosensory MMR (sMMR), a counterpart of auditory MMN, are sparse. Nonetheless, it is reliably obtained in adults (Kekoni et al., 1997; Shinozaki et al., 1998; Akatsuka et al., 2005; Spackman et al., 2010) and in healthy children (Restuccia et al., 2009). In these studies, the sMMR has been shown to be elicited in a response to changes or violations in stimulus site (different fingers) of an electric pulse, frequency or duration of a vibration burst or a within-pair inter-stimulus interval of stimulus pairs. In most studies, the sMMR has been elicited at about 100–200 ms after the stimulus onset over the fronto-central regions either as a negative or positive component, presumably depending on the direction of the generating dipole (Kekoni et al., 1997; Akatsuka et al., 2005). Spackman et al. (2007) found both a negative shift of a difference wave (deviant minus standard) at about 100–200 ms fronto-centrally contralateral to stimulus and a subsequent positive shift at about 150–250 ms with centro-parietal scalp

distribution, despite of the stimulus site. Correspondingly, Restuccia et al. (2009) found in children a central negative shift of the difference wave at about 120–180 ms contralateral to stimulus, followed by a deflection at about 180–250 ms, albeit negative in polarity and distributed frontally contralateral to stimulus. In a tactile two-point discrimination task (Akatsuka et al., 2007a,b) the generators of the magnetic equivalent of the sMMR [the magnetic mismatch field (MMF)], peaking around 30–70 ms and 150–250 ms, were found in the primary and secondary somatosensory cortex contralateral to stimulus, respectively. Studies with intracranial recordings using vibrotactile stimulation have showed that the sMMR is localized on the postcentral gyrus on the cortex (Spackman et al., 2010; Butler et al., 2011).

Contrary to studies in the auditory and visual modalities, to our knowledge, there are no studies showing the effects of normal aging on the pre-attentive detection of somatosensory changes. Nevertheless, Bolton and Staines (2012) have studied age-related changes in somatosensory ERPs using tasks that require subject's attentional resources. They suggested that in an attention-demanding somatosensory task age-related alterations in the attention mechanism are partly due to deficit in suppressing irrelevant sensory information. However, the elicitation of the sMMR does not rely on the subject's attention or reactions and it is thus a potentially valuable tool for clinical purposes. Indeed, it has been showed that the sMMR can be used reliably for neurophysiological evaluation of tactile two-point discrimination (Akatsuka et al., 2007a) or the severity of a cerebellar dysfunction (Restuccia et al., 2007; Chen et al., 2014).

We recorded ERPs to electrical pulses with changes in the location of the stimuli in hand in two groups of subjects, young and elderly adults, while they were attending to a task in the visual modality. We hypothesize that the sMMR is elicited at the scalp regions representing the primary and secondary somatosensory cortices at about 100–250 ms after the stimulus onset as reported earlier (Shinozaki et al., 1998; Restuccia et al., 2009). We also hypothesize that the sMMR is attenuated in amplitude in aged compared to young similarly as in the auditory MMN.

MATERIALS AND METHODS

PARTICIPANTS

Electroencephalogram was collected from 22 young (22–36 years) and 14 elderly (66–95 years) Finns. All participants were right-handed volunteers with no self-reported neurological or psychiatric conditions. Five of the participants were discarded due to disrupted data (e.g., excessive movement during the recording). For the final data analysis there were 18 participants in the young adults group (22–29 years old, mean age 25 years, six female) and 13 participants in the elderly group (66–95 years old, mean age 75 years, nine female). The elderly group comprised of volunteers from the local organization of retired people recruited at their weekly meeting after an informative presentation of the study. The young adults group comprised university students recruited via e-mail. An informed written consent was obtained from each participant. The experiment was undertaken in accordance with the Declaration of Helsinki. The ethical committee of the University of Jyväskylä had approved the study.

STIMULI AND PROCEDURE

During the recording, the subjects sat comfortably in a chair in a laboratory room. The subjects were instructed to ignore stimulation to the fingers and to be fully involved with a radio play, about which they were told to be asked questions afterward. The radio play was presented via loudspeaker placed about 50 cm above the subjects head with a volume subjectively comparable to normal speaking voice. The subjects were asked to fix their gaze at the cross on a computer screen placed about 1.5 m in front of the subject. The recording was video monitored from the room next to the subject's room to control the subject's sleepiness and movements during recording.

Electrical stimulation was generated with a constant current stimulator (Digitimer Ltd., model DS7A, Welwyn Garden City, UK). Electrical pulses of 200 μs in duration were delivered via conductive jelly moistened flexible metal ring electrodes (Technomed Europe Ltd., Maastrich, Netherlands) on the left forefinger and little finger (stimulating cathode above the proximal phalanx and anode above the distal phalanx). A piece of gauze was placed on the finger between electrodes to prevent conductivity between the two electrodes in the same finger. A run of 1000 stimuli was delivered with an inter-stimulus interval (ISI) of 500 ms. Frequently presented "standard" stimuli (probability 85%) were presented to one and rare "deviant" stimuli (probability 15%) to the other finger (forefinger and little finger). This assignment was counterbalanced between the subjects. Stimulus intensities were adjusted for each subject independently for both fingers to be twice the subjective sensory threshold, which was tested before recording. Overall, forefinger stimulus intensities were larger in the aged group (forefinger mean 5.5 mA, range 0.48–0.78 mA; little finger mean 4.4 mA, range 0.30–0.62 mA) than in the young group (forefinger mean 4.1 mA, range 0.28–0.56 mA; little finger mean 3.8 mA; range 0.24–0.48 mA) and larger to forefinger than to little finger within the both age groups: young $t_{17} = 3.50$, $p = 0.003$, $d = 0.500$; aged $t_{12} = 4.10$, $p = 0.003$, $d = 0.208$. One-way ANOVA showed a significant difference between the age groups in forefinger stimulus intensity ($F_{1,29} = 21.24$, $p < 0.001$), but no significant difference between little finger stimulus intensities ($F_{1,29} = 3.60$, $p = 0.068$).

EEG ACQUISITION

Electroencephalogram was recorded with Brain Vision Recorder software (Brain Products GmbH, Munich, Germany) at 30 scalp locations. Ag/AgCl electrodes were placed on the electrode cap (Easy Cap QA40) according to the modified International 10–20 System at FP1, FP2, Fz, F3, F4, F7, F8, FC1, FC2, FC5, FC6, T7, T8, C3, C4, Cz, CP1, CP2, CP3, CP4, CP5, CP6, Pz, P3, P4, P7, P8, Oz, O1, and O2. Linked left and right mastoid electrodes served as a reference for all electrodes. The ground electrode was placed in the middle of the forehead. Eye movements and blinks were measured from bipolar electrodes placed one above the left eye and another lateral to the right orbit. The signal was amplified (Brain Vision QuickAmp), filtered with a band pass of 0.1–100 Hz and stored on hard disk at a sampling rate of 1000 Hz.

DATA PROCESSING

The data were analyzed with Brain Vision Analyzer 2.0 software (Brain Products GmbH). The signals from the electrodes were first filtered with a band pass of 0.1–20 Hz (24 dB/octave roll off) and divided in stimulus onset-locked segments from −100 to +500 ms by stimulus type (deviant stimulus and standard stimulus immediately preceding the deviant stimuli). Segments with signal amplitude exceeding ±90 μV from the averaging and any recording channel were omitted from the further analysis. The pre-stimulus baseline was corrected by the mean amplitude between −100 to 0 ms. An average of 122 of standard (min = 79, max = 149, median = 131) and an average of 123 deviant (min = 64, max = 148, median = 128) trials were available for the further analysis from each individual.

Visual inspection indicated amplitude differences between standard and deviant responses for P50 and N80 components. Accordingly, the maximum peak amplitude value at C4 electrode (Shinozaki et al., 1998) and its latency were calculated within a time window of 30–80 ms and 40–110 ms after the onset of the stimulus for P50 and N80, respectively. To compare difference between the stimulus types and between the age groups, statistical analysis of ERP peak amplitudes of P50 and N80 were performed in repeated measures multivariate analysis of variance (MANOVA) with factors of Stimulus type (standard, deviant) and Age group (young, aged). In addition, visual inspection revealed MMR-like differential responses at 180–220 ms and 250–290 ms after the stimulus onset, labeled as early and late MMR, respectively. Accordingly, mean amplitude values from these time windows at nine electrode sites (FC1, Fz, FC2, C3, Cz, C4, P7, Pz, P8) were calculated. The selection of the electrode sites were based on the visual inspection of grand averaged scalp topography maps and previous findings on sMMR (Restuccia et al., 2009). MANOVA with within-subjects factors of Stimulus type (standard, deviant), Laterality (left: FC1, CP1, P7; medial: Fz, Cz, Pz; right: FC2, CP2, P8), Anteriority (frontal: FC1, Fz, FC2; central: CP1, Cz, CP2; parietal: P7, Pz, P8) and between-subjects factor of Age group (young, aged) were applied. Whenever group differences were found, differential ERPs (deviant minus standard responses) were calculated separately for both age groups and analysis of variances (ANOVA) was performed to compare differential responses between the groups. Finally, Pearson's correlation coefficients, controlled with age, were computed separately within the each age group to examine the relationship between the stimulus intensity and differential ERPs.

Effect size estimates are described as partial eta squared (η_p^2) scores for MANOVA and Cohen's d for t-tests. Paired samples t-tests were two tailed. The threshold for statistical significance was $p < 0.05$. Since focusing on the processing of different stimulus types, here we report only the main effects and interaction effects of MANOVA including the factor of Stimulus type.

RESULTS

Figures 1 and **2** depict the grand-averaged waveforms to deviant and standard stimuli and a differential waveform within each age group on analyzed electrode sites. The grand-averaged waveforms for P50 and N80 on C4 are shown in **Figure 3**.

P50

For P50 amplitude, a MANOVA showed a significant main effect of Stimulus type ($F_{1,29} = 6.13$, $p = 0.019$, $\eta_p^2 = 0.175$), but neither an interaction effect between Stimulus type and Age group ($F_{1,29} = 1.35$, $p = 0.254$, $\eta_p^2 = 0.045$) nor any other interaction effect with Stimulus type. Mean difference between the responses to deviant and standard stimuli was 0.42 μV (95% confidence interval 0.048–0.787 μV).

For P50 latency, all the effects were non-significant including the main effect of Stimulus type ($F_{1,29} = 0.12$, $p = 0.730$, $\eta_p^2 = 0.004$) and the interaction effect of Stimulus type × Age group ($F_{1,29} = 0.20$, $p = 0.656$, $\eta_p^2 = 0.007$).

N80

An effect of Stimulus type was significant ($F_{1,29} = 15.17$, $p = 0.001$, $\eta_p^2 = 0.343$). Mean difference between the responses to deviant and standard stimuli was −1.13 μV, 95% confidence interval −1.695 to −0.570 μV). An interaction effect of Stimulus type × Age group was non-significant ($F_{1,29} = 1.02$, $p = 0.322$, $\eta_p^2 = 0.034$) as were the other interaction effects. Negative correlations between the N80 amplitude to deviant stimuli and the stimulus intensity to forefinger ($r = -0.602$, $p < 0.001$) and to little finger ($r = -0.386$, $p = 0.035$) were found.

For the latency, no significant main effect of Stimulus type ($F_{1,29} = 1.23$, $p = 0.277$, $\eta_p^2 = 0.041$) was found, but there was a significant interaction effect between Stimulus type and Age group ($F_{1,29} = 6.73$, $p = 0.015$, $\eta_p^2 = 0.188$). Thus, the standard and deviant stimulus responses were compared separately within each age group. Among young, the response latency to deviant stimuli was prolonged compared to that to standard stimuli (mean latencies 80.8 and 75.2 ms, respectively), $t_{17} = 2.45$, $p = 0.025$, $d = 0.486$ (mean difference 5.6 ms, 95% confidence interval 0.8–10.3 ms). Within aged no difference between the peak latencies to different stimulus types was found ($t_{12} = 1.39$, $p = 0.189$, $d = 0.402$, mean difference −2.2 ms, 95% confidence interval −5.7 to 1.3 ms; mean latency for the deviant responses were 85.9 and 88.2 ms for the standard responses). Further, an ANOVA showed that responses to standards ($F_{1,29} = 10.02$, $p = 0.004$), but not to deviants ($F_{1,29} = 3.15$, $p = 0.088$), were prolonged in aged compared to young.

THE MMR

Figure 4 shows mean scalp potential maps for the differential responses (deviant minus standard stimulus responses) at the analyzed latency ranges. Correlation analysis (Pearson's, controlled with age, Bonferroni-adjusted) showed no correlation between the stimulus intensities to fingers and the amplitude values of differential responses for early or late MMR.

Early MMR: 180–220 ms

A MANOVA showed a significant main effect of Stimulus type ($F_{1,29} = 5.75$, $p = 0.023$, $\eta_p^2 = 0.165$) and interaction effects of Stimulus type × Laterality ($F_{2,28} = 7.92$, $p = 0.002$, $\eta_p^2 = 0.361$) and Stimulus type × Centrality ($F_{1,28} = 5.13$, $p = 0.013$, $\eta_p^2 = 0.268$), indicating inequality in scalp distributions of the ERP amplitudes to the different stimulus types (i.e., a mismatch response).

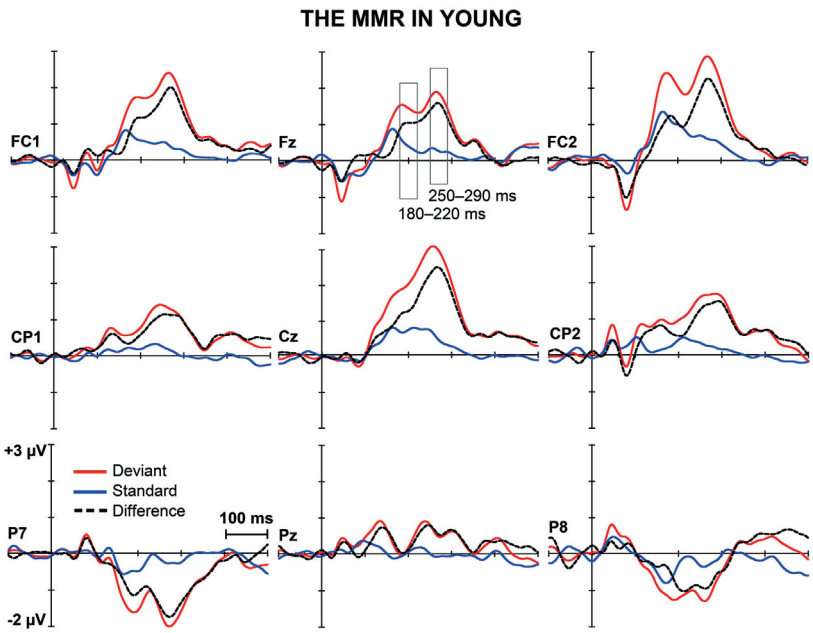

FIGURE 1 | The MMR in young. The grand-averaged waveforms to deviant and standard stimuli and a differential waveform (deviants minus standards) within young at electrode sites analyzed for the early and the late MMR.

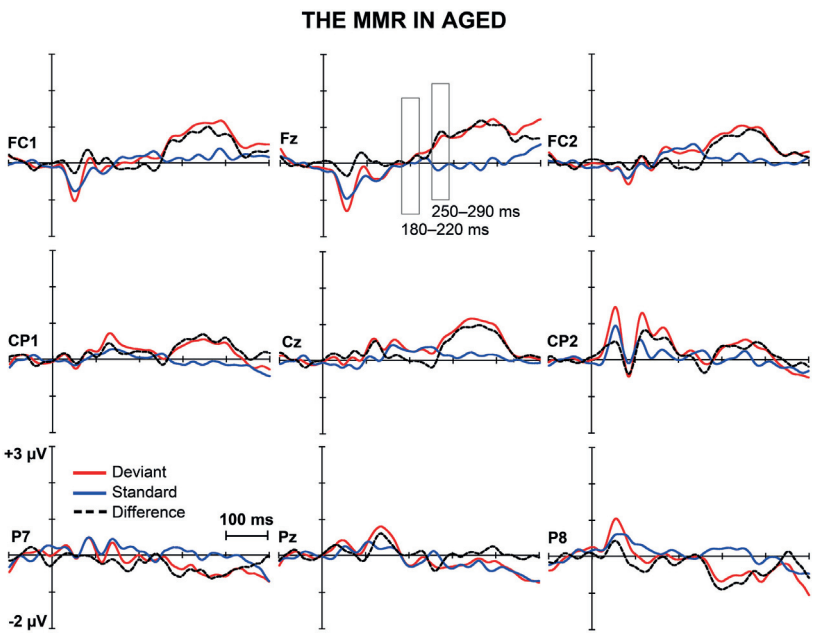

FIGURE 2 | The MMR in aged. The grand-averaged waveforms to deviant and standard stimuli and a differential waveform (deviants minus standards) within aged at electrode sites analyzed for the early and the late MMR.

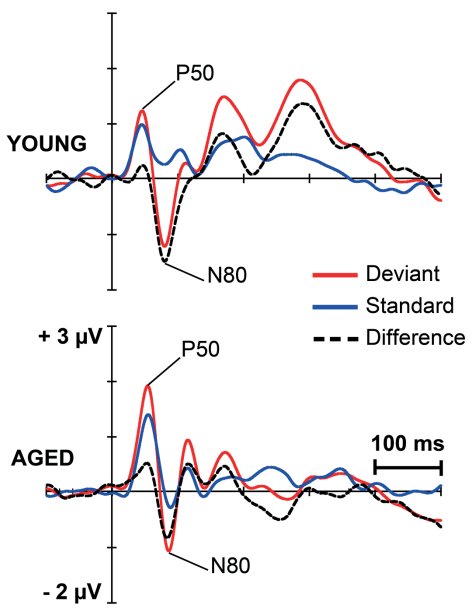

FIGURE 3 | The grand-averaged waveforms to deviant and standard stimuli and a differential waveform within each age group at electrode C4, where P50 and N80 were analyzed.

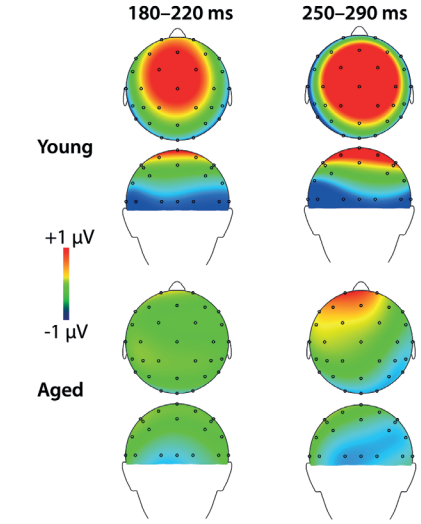

FIGURE 4 | The voltage distribution maps for the early and late MMR in young and aged.

In addition, significant interaction effects of Stimulus type × Age group ($F_{1,29} = 5.27$, $p = 0.029$, $\eta_p^2 = 0.154$) and Stimulus type × Laterality × Age group ($F_{2,28} = 4.08$, $p = 0.028$, $\eta_p^2 = 0.226$) were found, revealing unequal responses between the age groups and non-homogenous scalp distribution of the MMR between young and aged. Since Stimulus type × Centrality × Laterality × Age group ($F_{4,26} = 2.13$, $p = 0.106$, $\eta_p^2 = 0.247$) and Stimulus type × Centrality × Age group ($F_{2,28} = 3.01$, $p = 0.066$, $\eta_p^2 = 0.177$) showed no significant effect, amplitude values were averaged over left, medial and right electrode sites, and responses to standard and deviant stimuli were compared in paired samples t-tests separately within each age group. Within young, responses to deviant stimuli differed significantly to those of standard stimuli at medial electrode sites, $t_{17} = 3.57$, $p = 0.002$, $d = 1.033$. Differential responses to the two stimulus types at right hemisphere electrode sites, $t_{17} = 2.09$, $p = 0.052$, $d = 0.563$, and left hemisphere electrode sites, $t_{17} = 1.99$, $p = 0.063$, $d = 0.477$, did not reach the significance. Among aged the difference in amplitude between the ERPs to deviants and standards were not evident at any of the analyzed averaged electrode sites (medial: $t_{12} = 0.51$, $p = 0.616$, $d = 0.180$; left: $t_{12} = 0.35$, $p = 0.736$, $d = 0.093$; right: $t_{12} = 0.03$, $p = 0.981$, $d = 0.010$; **Table 1**).

The MMR was different in amplitude between the age groups at medial electrode sites ($F_{1,29} = 6.96$, $p = 0.013$), but not at left ($F_{1,29} = 2.93$, $p = 0.097$), neither at right ($F_{1,29} = 2.05$, $p = 0.163$)

Table 1 | Latency range of 180–220 ms.

Electrode pool	*t*	*P* (2-tailed)	*d*	Mean difference (μV)	95% CI lower	95% CI upper
Left/young	1.99	0.063	0.477	0.23	−0.014	0.479
Left/aged	−0.35	0.736	0.093	−0.02	−0.168	0.122
Medial/young	3.57	0.002	1.033	0.77	0.315	1.224
Medial/aged	0.51	0.616	0.180	0.06	−0.181	0.292
Right/young	2.09	0.052	0.563	0.26	−0.002	0.532
Right/aged	−0.03	0.981	0.010	−0.001	−0.293	0.286

Post hoc tests (paired samples t-tests) for the interaction effect Stimulus type × Laterality × Age group. CI, confidence interval. d, Cohen's d.

electrode sites. The differential mean amplitudes were larger in young (left 0.23 μV, middle 0.77 μV, right 0.26 μV) compared to aged (left −0.02 μV, middle 0.06 μV, right −0.001 μV; **Table 1**).

Late MMR: 250–290 ms

Figure 5 shows the mean amplitudes to deviant and standard responses, standard deviations and individual participants' amplitudes of the differential responses (deviant minus standard) in both age groups. A MANOVA revealed a significant main effect of Stimulus type ($F_{1,29} = 13.31$, $p = 0.001$, $\eta_p^2 = 0.315$) and significance for the all interaction effects including the factor of Stimulus type: Stimulus type × Laterality ($F_{2,22} = 11.33$, $p = 0.0001$, $\eta_p^2 = 0.447$), Stimulus type × Centrality ($F_{2,22} = 9.22$, $p = 0.001$, $\eta_p^2 = 0.397$), Stimulus type × Laterality × Centrality ($F_{4,26} = 4.30$, $p = 0.008$, $\eta_p^2 = 0.398$), Stimulus type × Age group ($F_{1,29} = 8.96$, $p = 0.006$, $\eta_p^2 = 0.236$), Stimulus type × Laterality × Age group ($F_{2,28} = 5.90$, $p = 0.007$, $\eta_p^2 = 0.296$), Stimulus type × Centrality × Age group ($F_{2,28} = 5.61$, $p = 0.009$, $\eta_p^2 = 0.286$), and Stimulus type × Laterality × Centrality × Age group ($F_{4,26} = 4.41$, $p = 0.007$, $\eta_p^2 = 0.404$). The 4-tailed interaction indicates an unequal scalp distribution of the MMR between the age groups. The subsequent paired samples *t*-tests comparing the standard and deviant stimulus responses were applied separately on each analyzed electrode site and for both age groups (**Table 2**). Within young the difference in amplitude between the ERPs to deviant and standard stimuli were significant at FC1, Fz, FC2, CP1, Cz, CP2, P7, P8 ($t_{17} = 6.28$–4.66, $p < 0.001$–0.045, $d = 0.690$–1.575). Within aged, instead, ERPs to deviant and standard stimuli differed significantly only at Fz ($t_{12} = 3.53$, $p = 0.004$, $d = 0.972$).

The MMR (deviant minus standard differential response) was different in amplitude between the age groups at FC1 ($F_{1,29} = 5.91$, $p = 0.022$), FC2 ($F_{1,29} = 8.31$, $p = 0.007$), CP1 ($F_{1,29} = 6.12$, $p = 0.019$), Cz ($F_{1,29} = 10.87$, $p = 0.003$), CP2 ($F_{1,29} = 10.87$, $p = 0.003$), P7 ($F_{1,29} = 13.38$, $p = 0.001$), Pz ($F_{1,29} = 5.24$, $p = 0.030$), but not at Fz ($F_{1,29} = 1.17$, $p = 0.289$) neither at P8 ($F_{1,29} = 0.307$, $p = 0.584$; **Table 2**).

DISCUSSION

We recorded ERPs to changes in somatosensory stimuli, i.e., electrical pulses to different fingers in healthy young and elderly adults in a passive oddball condition. The sMMR was positive in polarity and elicited at two latency ranges in young: centro-parietally at 180–220 and fronto-centrally at 250–290 ms after the stimulus

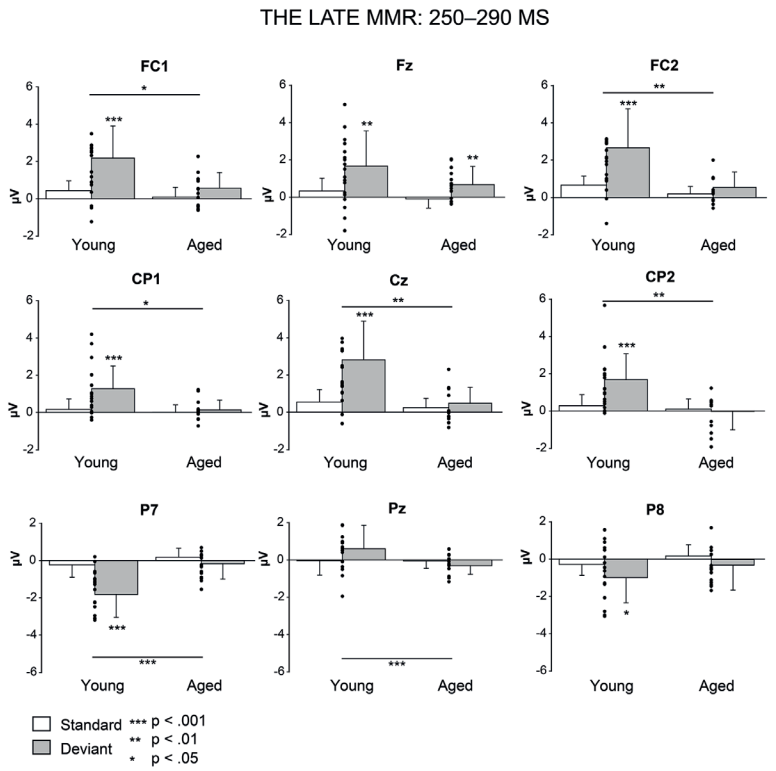

FIGURE 5 | Mean amplitudes and standard deviations to deviant and standard stimuli responses on analyzed electrode sites in young and aged. Values of the differential response (deviants minus standards, i.e., MMR) of the individual participants' are shown as scatterplots.

Table 2 | Latency range of 250–290 ms.

Electrode site/age group	*t*	*P* (2-tailed)	*d*	Mean difference (μV)	95% CI lower	95% CI upper
FC1/young	4.30	<0.001	1.375	1.75	0.890	2.602
FC1/aged	2.00	0.069	0.685	0.48	−0.043	−0.017
Fz/young	3.24	0.005	0.932	1.33	0.464	2.199
Fz/aged	3.53	0.004	0.972	0.77	0.294	1.245
FC2/young	4.36	<0.001	1.320	2.01	1.035	2.979
FC2/aged	1.74	0.107	0.558	0.36	−0.090	0.807
CP1/young	3.56	0.002	1.154	1.10	0.450	1.756
CP1/aged	0.93	0.370	0.308	0.14	−0.191	0.477
Cz/young	4.66	<0.001	1.473	2.26	1.237	3.285
Cz/aged	0.93	0.370	0.337	0.24	−0.320	0.798
CP2/young	4.11	0.001	1.301	1.39	0.677	2.107
CP2/aged	−0.46	0.651	0.155	−0.12	−0.704	0.457
P7/young	−6.28	<0.001	1.595	−1.59	−2.122	−1.054
P7/aged	−1.80	0.097	0.511	−0.34	−0.761	0.072
Pz/young	2.05	0.057	0.612	0.64	−0.020	1.298
Pz/aged	−1.74	0.107	0.571	−0.25	−0.564	0.063
P8/young	2.00	0.045	0.690	−0.72	−1.414	−0.017
P8/aged	−1.70	0.114	0.507	−0.46	−1.058	0.130

Paired samples t-tests (deviant vs. standard stimulus responses). CI, confidence interval. d, Cohen's d.

onset. In aged, the sMMR was attenuated and elicited only at the latter latency window with reduced scalp distribution compared to young. While in elderly the sMMR was evident only at Fz, it was found widely at fronto-central electrodes in young participants.

The sMMR to location changes has been found earlier by Shinozaki et al. (1998) in young adults. In addition, there are corresponding results in children (Restuccia et al., 2009). Shinozaki et al. (1998) found a central positive deflection to middle or index finger deviants at 100–200 ms post-stimulus, compatible to the early sMMR found in the present study. However, they did not report the following frontal positivity that was found in our study both in young and aged, probably owing to linked ear lobes reference used in their study compared with the average reference of the present study. Chen et al. (2014) argued in light of their findings that the sMMR is less sensitive to changes in location than to duration: they reported fronto-central negativity to vibrotactile duration deviants at 150–250 ms, but did not find sMMR to location changes. They suggested that the sMMR to spatially separated stimuli was absent due to relatively high age (mean 57.5 years) of their participants or too low stimulus intensity used in their study. In our data the late sMMR were found in aged despite of notably older age of the participants (mean age 75 years) than in the study of Chen et al. (2014), albeit the stimulus intensities were higher in our study, too. However, we found no correlation between the stimulus intensity and the sMMR amplitude though we did not specifically test extreme stimulus intensities.

In addition to the early sMMR (180–220 ms) found in young adults there was also a differential response at later latency range (250–290 ms) which was significant in both age groups. A few earlier studies have found sMMR in two latency ranges, albeit the findings seem somewhat discrepant. Akatsuka et al. (2005) reported a sMMR to temporal discrimination deviants eliciting an early negativity and a positive deflection at 100–200 ms post-stimulus. Spackman et al. (2007) found instead a negative fronto-central shift of a difference wave at 100–200 ms followed by a centro-parietal positive shift at 150–250 ms to vibrotactile presented changes in duration and frequency. The latter was suggested to reflect a process that is specific to sensory discrimination in the somatosensory modality. Similarly, Butler et al. (2011) reported a sMMR of negative polarity to duration changes approximately peaking at 145 ms followed with a fronto-central sMMR of positive polarity peaking at 235 ms post-stimulus. The late sMMR found in the present study seems to be similar in scalp topography and only slightly later in latency compared to the sMMR reported by Butler et al. (2011).

To our knowledge, the present study is the first to show the reduction of the sMMR in healthy aging. The results are in line with the findings of the auditory MMN. A recent meta-analysis concluded that the MMN to frequency and duration changes considerably declines in normal aging (Cheng et al., 2013). There is evidence from auditory studies linking the reduction of the MMN amplitude to decline in modality specific cognitive processing (Kisley et al., 2005; Mowszowski et al., 2012; Foster et al., 2013) and amnestic mild cognitive impairment (Lindin et al., 2013). Also the visual MMN to changes in motion direction and object

form have been reported to diminish in aging, analogously to the auditory MMN (Tales et al., 2002; Lorenzo-Lopez et al., 2004). In addition, it has been shown that the latency of the auditory MMN to frequency (Gaeta et al., 2001) and temporal (Bertoli et al., 2002) changes is prolonged in aging.

A possible explanation for the aging-related diminution of the MMR may also lie behind disturbed predictive coding of sensory information. The predictive coding models presume that the brain continuously updates an internal model of environment by synaptic plasticity to predict the causes of sensory input; the MMN represents an inconsistency between the predicted sensory input (repetitive standards) and the unlearned (deviant) stimulus (Friston, 2005; Garrido et al., 2009; Wacongne et al., 2012). Further, *N*-methyl-D-aspartate (NMDA) receptor, a predominant controller of synaptic plasticity and memory function, have been proposed to have a fundamental role in predictive coding and the MMN generation (Tikhonravov et al., 2008, 2010; Wacongne et al., 2012). Aging-related deficiency in NMDA function may thus at least partly explain the MMN reduction in aging (Muller et al., 1994; Näätänen et al., 2011). It is also possible that in aging, predictive coding of stimulus characteristics is interfered by declined gating of sensory inputs (Chao and Knight, 1997) due to reduced inhibitory function (Reuter-Lorenz and Park, 2010; Bolton and Staines, 2012) in the sensory cortices (David-Jurgens and Dinse, 2010; Cheng and Lin, 2013). The assumption of age-related deficit in suppression of irrelevant sensory stimuli cannot be tested in the present data which was not designed to study the above-mentioned mechanism (see, e.g., Kisley et al., 2005). Nevertheless, we found age-related prolongation of the N80 latency (see **Figure 3**) indicating that aging might also have an effect on early sensory processing that precede the higher order sensory-cognitive functions.

There are limitations in the present study that future studies can address. First, the relationship between the age-related reduction of the sMMR and the cognitive function should be confirmed by using neuropsychological test batteries and carefully controlled demographic information (e.g., lifestyle factors and educational level). Second, we did not apply any control condition in order to investigate the underlying neural mechanism of sMMR (for a review of underlying mechanism of the auditory MMN, see Näätänen et al., 2005). Third, a low amount of sensors used in the EEG recording of the present study did not enable the application of source localization in the present data. Thus, no inferences of the processing hierarchy or pathways of the sMMR generation in the cortex can be made. Finally, although the preliminary results of the present study clearly demonstrate age-related effects to somatosensory deviance detection, our findings should be confirmed in future studies with larger sample sizes, and wide-ranging age range of participants, in order to determine whether the effects of aging on sensory-cognitive processing are constant within the adult life span.

In conclusion, the present study showed that the sMMR to location changes is sensitive to aging. The sMMR was attenuated in amplitude and prolonged in latency in aged compared to young adults. The findings provide new knowledge for the scant literature on aging-related changes in pre-attentive sensory-cognitive processing in the somatosensory modality.

AUTHOR CONTRIBUTIONS

Juho M. Strömmer, Ina M. Tarkka and Piia Astikainen designed the experiment. Juho M. Strömmer recorded and analyzed the data. The interpretation of data was done by Piia Astikainen, Ina M. Tarkka and Juho M. Strömmer. The manuscript was prepared by Juho M. Strömmer and revised by Piia Astikainen and Ina M. Tarkka. All of the authors approve the final version of the manuscript to be published.

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II

AUTOMATIC AUDITORY AND SOMATOSENSORY BRAIN RESPONSES IN RELATION TO COGNITIVE ABILITIES AND PHYSICAL FITNESS IN OLDER ADULTS

by

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Automatic auditory and somatosensory brain responses in relation to cognitive abilities and physical fitness in older adults

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In normal ageing, structural and functional changes in the brain lead to an altered processing of sensory stimuli and to changes in cognitive functions. The link between changes in sensory processing and cognition is not well understood, but physical fitness is suggested to be beneficial for both. We recorded event-related potentials to somatosensory and auditory stimuli in a passive change detection paradigm from 81 older and 38 young women and investigated their associations with cognitive performance. In older adults also associations to physical fitness were studied. The somatosensory mismatch response was attenuated in older adults and it associated with executive functions. Somatosensory P3a did not show group differences, but in older adults, it associated with physical fitness. Auditory N1 and P2 responses to repetitive stimuli were larger in amplitude in older than in young adults. There were no group differences in the auditory mismatch negativity, but it associated with working memory capacity in young but not in older adults. Our results indicate that in ageing, changes in stimulus encoding and deviance detection are observable in electrophysiological responses to task-irrelevant somatosensory and auditory stimuli, and the higher somatosensory response amplitudes are associated with better executive functions and physical fitness.

Normal ageing is accompanied by a degeneration of brain structure[1] and changes in sensory processing, memory, and executive functions[2,3]. Age-related atrophy of brain tissue, together with changes in neural transmission, result in a reorganisation of neural circuits and compensatory brain activity, which eventually leads to alterations in cognitive performance[3,4]. Since the changes in the nervous system precede those in behaviour, event-related potentials (ERPs) that reflect the brain's sensory-cognitive functions are promising tools to detect early ageing-related cognitive deterioration[5].

Mismatch negativity (MMN), which is an automatic ERP response to stimulus changes, indexes cognitive decline in normal ageing as well as in different neuropsychiatric, neurological, and neurodevelopmental disorders[6,7]. The MMN is elicited in the oddball condition, where rare deviant stimuli are interspersed with repetitive standard stimuli[8]. The change detection the MMN reflects is based on the comparison process between the memory trace formed by the standard stimuli and deviant stimulus input[9]. The MMN occurs usually 150–250 ms post-stimulus[8]. The MMN was first discovered in the auditory sensory modality[10], and changes in stimulus intensity, frequency, or location are reflected by the MMN amplitude[9]. The MMN has also been demonstrated to respond to changes in somatosensory[11–14], visual[15,16], and olfactory[17] stimuli.

In the auditory modality, changes in stimulus duration and frequency have primarily been used to study age-related alterations in sensory processing[18]. The auditory MMN (aMMN) amplitude to changes in frequency[19–21] and duration[21,22] is attenuated in older adults compared to young adults. The amplitude of aMMN related to changes in stimulus duration and inter-stimulus intervals may be associated with impaired cognitive performance, especially in verbal memory and executive functions[23–25].

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	Mean amplitude (μV) ± SD		Mean difference	Age group main effect			Age group effect with stimulus intensities as covariates		
	Young	Older	Mean [SEM]	*F (df, error df)*	*p*	η_p^2	*F (df, error df)*	*p*	η_p^2
P50									
std	0.58 ± 0.45	0.83 ± 0.60	0.23 [0.10]	4.57 (1,117)	0.035*	0.038	0.03 (1,115)	0.863	<0.001
dev	0.82 ± 0.51	1.24 ± 0. 75	0.42 [0.12]	9.55 (1,117)	0.002**	0.075	0.30 (1,115)	0.592	0.003
N80									
std	0.06 ± 0.41	0.42 ± 0.48	0.37 [0.08]	16.77 (1,117)	<0.001***	0.125	3.26 (1,115)	0.074	0.028
dev	0.30 ± 0.70	0.62 ± 0.61	0.32 [0.13]	6.56 (1,117)	0.012*	0.053	0.88 (1,115)	0.350	0.008

Table 1. Results of ANCOVA of early somatosensory ERP components in response to deviant and standard stimuli in younger and older adult groups. Stimulus intensities for little finger and forefinger were used as covariates. SEM, standard error of mean; SD, standard deviation; df, degrees of freedom; η_p^2, partial eta squared; *p*, statistical significance; *p < 0.05; **p < 0.01; ***p < 0.001.

	Age group Main effect			Stimulus type Main effect			Stimulus type × Age group Interaction		
	F (df, error df)	*p*	η_p^2	*F (df, error df)*	*p*	η_p^2	*F (df, error df)*	*p*	η_p^2
sMMR	2.73 (1,117)	<0.001***	0.023	24.57 (1,117)	<0.001***	0.174	5.24 (1,117)	0.024*	0.043
sP3a	0.32 (1,117)	0.575	0.316	83,40 (1,117)	<0.001***	0.416	0.12 (1,117)	0.730	0.001
aN1	16.52 (1,117)	<0.001***	0.124	324.09 (1,117)	<0.001***	0.735	10.63 (1,117)	0.001***	0.083
aMMN	1.93 (1,117)	0.168	0.016	127.35 (1,117)	<0.001***	0.521	0.37 (1,117)	0.541	0.003
aP2	1.72 (1,117)	0.192	0.015	44.20 (1,117)	<0.001***	0.274	11.65 (1,117)	0.001***	0.091

Table 2. Results of the two-way repeated measures MANOVA of later somatosensory and auditory ERP components in response to deviant and standard stimuli in young and older adult groups. Df, degrees of freedom; η_p^2, partial eta squared; *p*, statistical significance; *p < 0.05; **p < 0.01; ***p < 0.001.

Somatosensory change detection paradigms and their associations with ageing are less studied than their auditory counterparts. Only one study has applied the somatosensory mismatch response (sMMR) to investigate pre-attentive change detection in older adults. In the study, it was found that the sMMR to electrical pulses applied to different fingers was altered in a group of healthy older adults compared to young adults[26]. The sMMR was evident in young adults in early and late latency ranges (180–220 ms and 250–290 ms after stimulus onset, respectively), while the early sMMR was absent and the late sMMR was attenuated in older adults.

In addition to MMN, other ERP components elicited in the passive oddball condition—N1, P2, and P3a—are shown to be sensitive to ageing[27–29]. Auditory N1 reflects automatic stimulus encoding and is elicited in the auditory cortex approximately 100 ms after tone onset[30]. A recent study reported increased N1 responses to repetitive standard stimuli in older compared to young adults, reflecting an age-related decrease in sensory inhibition[31]. P2, which is mostly studied in the auditory modality and typically peaks at around 150–250 ms post-stimulus, is involved in stimulus classification and the processing of task-irrelevant stimuli[32,33]. The effects of ageing on P2 are inconclusive. Notably, the only study reporting ageing-related decrease of P2 amplitude to frequency changes[34] used a passive oddball condition, where stimuli are outside of the attention of the participant. The studies reporting the opposite effects[35,36] or no effects related to ageing[37,38] used active oddball tasks, where the stimuli are attended to. In a passive oddball condition, P3a peaks at approximately 250–500 ms and usually has a fronto-central scalp topography. This reflects the automatic re-orienting of attention that follows the pre-attentive change detection and may also include conscious recognition of the stimuli[28]. In normal ageing, auditory P3a amplitude typically decreases[22,39,40], and its latency increases[41].

Here, we compared the brain responses of 38 young adults and 81 older adults to study the effects of ageing on sensory-cognitive functions in a passive change detection paradigm in the auditory and somatosensory modality. All participants performed a cognitive assessment, and the older adults also participated in a physical fitness measurement. Previous literature suggests that higher physical activity is linked to better cognitive performance[42] and to better cortical sensory processing reflected by ERPs[43–45] in older adults. Thus far, no ageing study has combined ERPs, cognition, and objective measures of physical fitness, making the current study the first in the field.

We hypothesised that sMMR[26] and aMMN[18] are diminished in amplitude in older participants compared to those in young participants. A similar attenuation of amplitude could be found for ERP components following aMMN/sMMR, namely, P2 and P3a[22,34]. We also hypothesised that ERPs correlate with cognitive test scores[23,24]. In older adults, we expected better physical fitness, especially aerobic fitness[46], to be associated with better cognitive performance and less attenuated ERP amplitudes, since physical activity and fitness may mitigate ageing-related cognitive decline[46,47].

Results

Early somatosensory ERP components. P50 and N80 peak amplitudes were analysed due to apparent differences in grand-average waveforms between the age groups (Fig. 1). The mean amplitude of P50 and

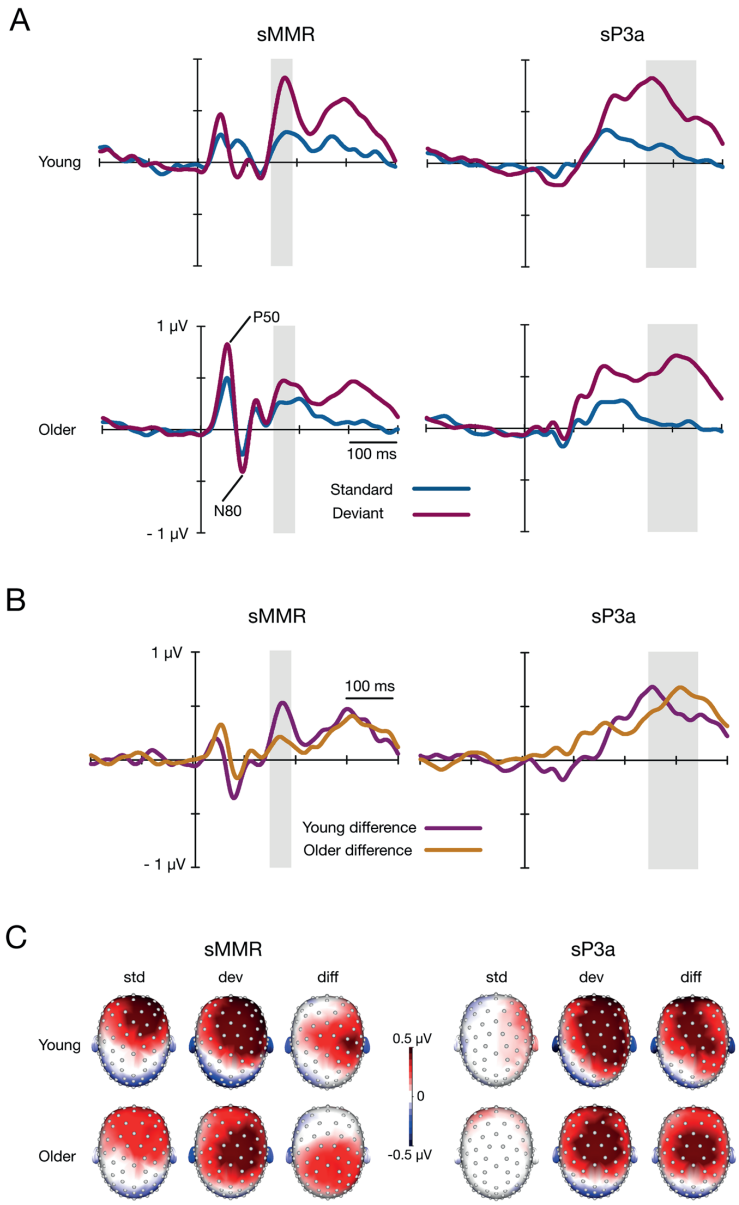

Figure 1. (**A**) Grand-averaged ERPs to somatosensory standard and deviant stimuli for young and older adults and (**B**) the differential waveforms (standard minus deviant) for young and older adults. Waveforms represent averages of the electrode pools applied in the analyses. The grey area shows the latency range of 153–193 ms for sMMR and of 258–358 for sP3a, from where the averaged amplitude values were extracted to analyse each ERP component. (**C**) The scalp voltage distributions of responses to standard (std) and deviant (dev) stimuli and differential responses (diff) (deviants minus standards). The topographic maps are shown as average voltages from 153–193 ms for sMMR and from 258–358 for sP3a. Note, due to keeping the scaling equal throughout, the lateralisation of differential response in older adults is no longer observable in the scalp topography of sMMR.

N80 were larger in older participants than in young participants for both standard and deviant stimuli (Table 1, Fig. 1a). Within both age groups, the amplitudes of P50 and N80 were larger for deviants than for standards. The age differences on P50 and N80 were not significant after controlling for the stimulus intensities, indicating that the group differences are due to higher stimulus intensities in older adults than in young adults (Table 1). The

	Mean amplitude (μV) ± SD		Difference between young adults and older adults				
	Young	Older	Mean [SEM]	*95% CI*	*t (df)*	*p*	*d*
sMMR							
std	0.26 ± 0.40	0.26 ± 0.35	<0.01 [0.07]	−0.14 to 0.15	0.01 (117)	0.992	0.02
dev	0.70 ± 0.74	0.42 ± 0.63	0.28 [0.14]	0.01 to 0.56	2.16 (117)	0.043*	0.40
aN1							
std	0.62 ± 0.74	−0.16 ± 0.70	0.78 [0.15]	0.48 to 1.08	5.54 (117)	0.001***	1.02
dev	−0.11 ± 0.72	−1.36 ± 0.85	0.25 [0.15]	−0.06 to 0.53	1.57 (117)	0.105	0.30
aP2							
std	−0.18 ± 0.45	0.18 ± 0.39	0.36 [0.08]	0.19 to 0.52	4.48 (117)	0.001***	0.83
dev	0.60 ± 0.83	0.43 ± 0.56	0.16 [0.15]	−0.12 to 0.47	1.27 (117)	0.298	0.23

Table 3. Mean amplitude values and standard deviantions and results of the independent samples *t*-tests (two-tailed, bootstrapped with 1000 iterations) comparing the response amplitudes between the groups of young and older adults in the later somatosensory and auditory ERP components in response to standard and deviant stimuli. SEM, standard error of mean; SD, standard deviation; CI, confidence interval; *d*, Cohen's *d*; df, degrees of freedom; *p*, statistical significance; *p < 0.05; **p < 0.01; ***p < 0.001.

latency of the P50 deviant stimuli response was prolonged in older participants compared to young participants, as follows: mean for young adults, 47 ± 9 ms; mean for older adults, 51 ± 7 ms; mean difference between the groups, 4.0 ms; standard error of mean (SEM), 1.7; F = 6.78, df = 1, df error = 117; $p = 0.010$, partial eta squared (η_p^2) = 0.055. This result remained significant after controlling for stimulus intensities, as follows: F = 4.22, df = 1, df error = 115; $p = 0.042$, $\eta_p^2 = 0.035$. No other effects on latency were found.

Later somatosensory and auditory ERP components. Topographic maps for somatosensory responses (Fig. 1) show a positive polarity sMMR[26] and sP3a[28] similar to those reported earlier in the somatosensory modality[12,13,26]. sMMR topography illustrated contralaterally localised positivity for standard and deviant stimuli in both age groups although lower amplitude in the older group. In the group of young adults, both sMMR and sP3a to deviant stimuli elicited activity at fronto-central electrode sites, while in the older adults the activation was prominent only in central electrode sites.

Topographic maps for the auditory responses show typical aN1[31], aMMN[8], and aP2[33] responses with most of the activity in the frontal electrode sites (Fig. 2). There were no clearly observable differences in auditory grand-averaged topographies between the groups other than those caused by an amplitude difference in the standard response (Fig. 2).

A two-way repeated measures multivariate analysis of variance (MANOVA) revealed the main effect of age group for amplitude values in the sMMR time window (mean for young adults, 0.48 μV; mean for older adults, 0.36 μV; amplitude values averaged for the standard and deviant stimuli) and aN1 time window (mean for young adults, 0.25 μV; mean for older adults −0.76 μV; amplitude values averaged for the standard and deviant stimuli) (Table 2, Figs 1 and 2). For all components—sMMR, sP3a, aN1, aMMN, and aP2ta—the main effect of stimulus type was found, indicating that the amplitudes to the deviant stimuli were larger than those to the standard stimuli for all components (Table 3, Figs 1 and 2). An interaction effect of stimulus type × age group was found for sMMR, aN1, and aP2 (Table 2, Figs 1 and 2). The following independent samples *t*-tests (two-tailed, bootstrap statistics) showed that the deviant responses in the sMMR analysis window were attenuated and that the standard responses for aN1 and aP2 were enlarged in older adults compared to young adults (Table 3). The interaction effect of stimulus type × age group for sMMR remained significant after controlling for stimulus intensity ($p = 0.019$); similarly, the interaction effect for aP2 was significant when controlling for hearing threshold ($p = 0.005$), but hearing threshold as a covariate decreased the *p* value of the interaction effect of stimulus type × age group for aN1 ($p = 0.055$).

Relationships between ERPs, cognitive test scores, and physical fitness measures. Table 4 illustrates the significant correlations within 95% and 99% confidence intervals (CIs). In older adults, the most robust positive correlations (within 99% CI) were found between sMMR and executive functions and between sP3a and walk test performance. These correlations in older adults remain significant ($p < 0.05$, 99% CI does not include zero) after controlling for age but not for education. Within the young adult group, a robust positive correlation was found between the aMMN and working memory, which remained significant after controlling for age and education (Table 4). In older adults, aMMN correlated neither with any of the cognitive measures nor with physical fitness measures.

The walk test performance had a robust negative correlation with total body fat percentage in older adults (two-tailed Pearson's r = −0.523, n = 79, $p < 0.001$, 99% CIs = −0.732 to −0.267) and body mass index (BMI) (n = 79, r = −0.462, $p < 0.001$, 99% CIs = −0.683 to −0.199) and positively correlated with the self-reported weekly physical activity hours (Spearman's rho = 0.481, n = 74, $p < 0.001$, 99% CIs = 0.220–0.687).

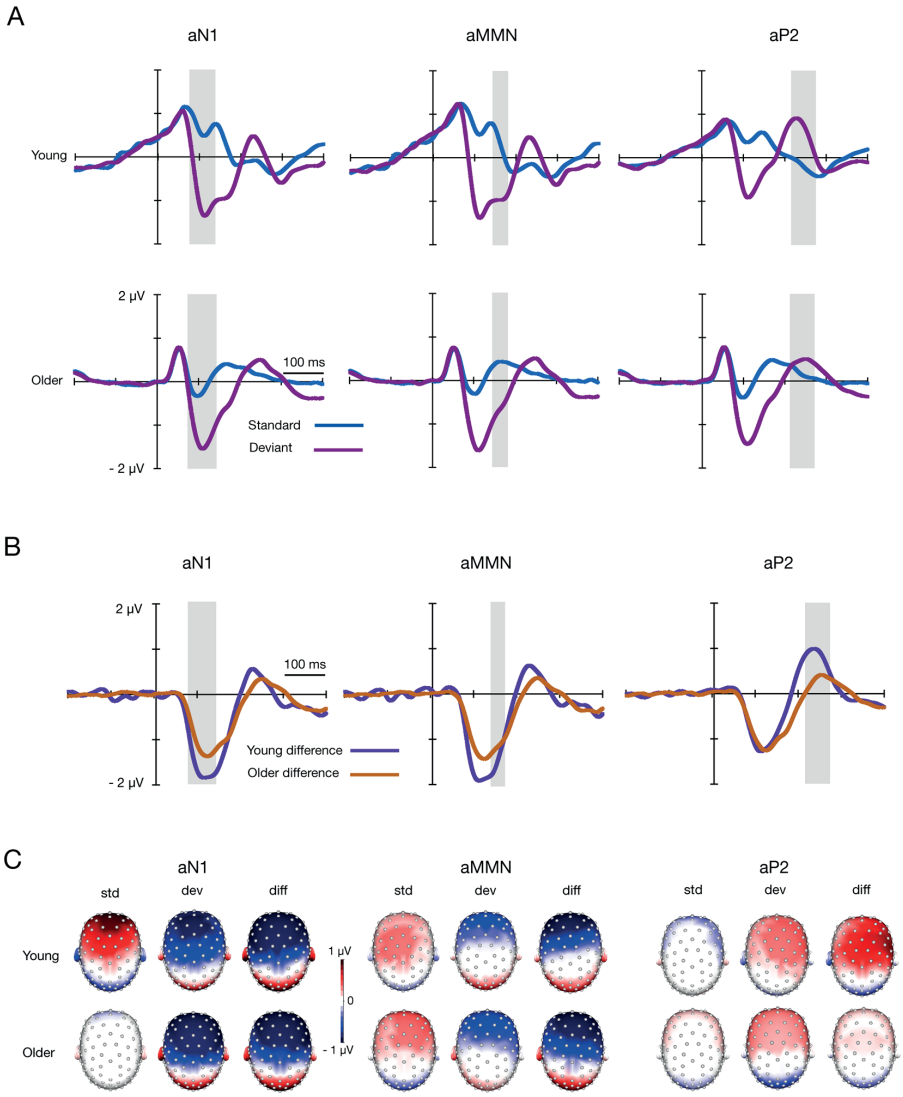

Figure 2. (**A**) Grand-averaged ERPs to auditory standard and deviant stimuli for young and older adults and (**B**) the differential waveforms (standard minus deviant) for young and older adults. Waveforms represent averages of the electrode pools applied in the analyses. The grey area shows the latency range of 88–138 ms for aN1, of 139–189 ms for aMMN, and of 208–280 ms for aP2, from where the averaged amplitude values were extracted to analyse each ERP component. (**C**) The scalp voltage distributions of responses to standard (std) and deviant (dev) stimuli and differential responses (diff) (deviant minus standard). The topography maps are shown as average voltages from 88–138 ms for aN1, 139–189 ms for aMMN, and 208–280 ms for aP2.

Discussion

We measured the ERPs to auditory frequency and somatosensory location changes in an ignore condition in young and older adults. The somatosensory P50, N80, and sMMR and the auditory aN1 and aP2 differed in amplitude between the groups. As expected, within the older group, higher sMMR amplitude showed a robust association with better executive functions, and higher sP3 amplitude was associated with longer walking distance (CI 99%, Table 4). There were also correlations between the auditory brain responses and tapping speed and explicit memory within the older group, but these associations were less robust (CI 95%, Table 4).

Somatosensory MMR was observed as a shift toward positive polarity at 153–193 ms in both age groups, which is in line with prior findings[11–13]. The differential response was larger in the young group than in the older group due to a larger deviant stimulus response amplitude in the young group, as was found in our earlier study[26],

Test	Older adults					Young adults			
	Variable	*r*	*p*	*99% CI*	*95% CI*	*r*	*p*	*99% CI*	*95% CI*
Executive function PC	sMMR (age)	0.299*	0.004	0.001 to 0.594	0.035 to 0.524	*ns*	*ns*	*ns*	*ns*
	sP3a	0.239	0.017	−0.062 to 0.517	0.003 to 0.468	*ns*	*ns*	*ns*	*ns*
	Six-minute walk distance (age, edu)	0.203	0.036	−0.076 to 0.443	0.011 to 0.395	—	—	—	—
Error susceptibility PC	sMMR (edu, age)	−0.276	0.007	−0.491 to 0.021	−0.465 to −0.055	*ns*	*ns*	*ns*	*ns*
Explicit memory PC	aP2 (age, edu)	0.254	0.012	−0.025 to 0.508	0.025 to 0.439	*ns*	*ns*	*ns*	*ns*
Working memory PC	aMMN	*ns*	*ns*	*ns*	*ns*	0.479*	0.001	0.045 to 0.756	0.184 to 0.689
Six-minute walk distance	sP3a (age)	0.319*	0.002	0.062 to 0.548	0.131 to 0.502	—	—	—	—
	Executive function PC (age, edu)	0.284	0.006	−0.050 to 0.531	0.059 to 0.490	—	—	—	—
	sMMR (edu)	0.203	0.036	−0.076 to 0.443	0.011 to 0.395	—	—	—	—
Tapping speed – dominant hand	sP3a	0.272	0.008	−0.009 to 0.533	0.034 to 0.478	*ns*	*ns*	*ns*	*ns*
	sMMR	0.215	0.028	−0.064 to 0.463	0.017 to 0.393	*ns*	*ns*	*ns*	*ns*
	aMMN (age)	−0.229	0.021	−0.477 to 0.033	−0.417 to −0.032	0.417	0.005	−0.026 to 0.715	0.116 to 0.658
Tapping speed – non-dominant hand	sP3a (age)	0.298	0.004	−0.019 to 0.600	0.067 to 0.520	*ns*	*ns*	*ns*	*ns*
	aN1 (age)	−0.252	0.013	−0.481 to 0.009	−0.436 to −0.058	*ns*	*ns*	*ns*	*ns*
	aMMN	*ns*	*ns*	*ns*	*ns*	0.387	0.008	−0.049 to 0.668	0.087 to 0.622

Table 4. Correlations between cognitive and physical measures and ERPs. Variables that show correlation at least in one of the groups within 95% CI are listed; those showing significant correlation within 99% CI are marked with *. Age and/or education (edu) in parentheses refers to significant partial correlations after controlling for the mentioned variable. *r*, Pearson's correlation coefficient (bootstrap statistics with 1000 iterations); *p*, significance (one-tailed); *CI*, confidence interval; *ns*, non–significant; —, not measured within the young adult group.

probably indicating attenuated deviance detection in older adults. Since the deviance detection the mismatch response reflects is suggested to be a cortical process[9], the changes in the sMMR can be expected to be related to the function of the somatosensory cortex. For sP3a, no group differences were found, and the deviant vs. standard differential response was significant in both groups. The pattern of results in the somatosensory modality showing attenuated sMMR, but no changes in amplitude of sP3 suggest that change detection, but not the following automatic shift of attention, is affected in ageing. It is notable, however, that the response latency of sP3a seems to be delayed in the older adults compared to young adults, but the data did not allow a valid statistical analysis to investigate this difference since there were no clear peak for sP3a for each individual, and mean amplitude values were thus applied in the analysis.

In addition to longer latency components, the amplitudes of the early somatosensory P50 and N80 were also larger in the older group than in the young group. This was mainly explained by higher sensory thresholds and thus higher stimulus intensities in older than younger participants. The result cannot be directly compared with the previous results where stimulus conditions (oddball vs. paired-pulse condition) and stimulus properties have been different between the studies[48–50]. Previous studies that have applied paired-pulse stimulus conditions have reported an ageing-related decline in cortical inhibition accompanied with behavioural inhibitory dysfunction[48–50].

Auditory N1 and P2 were affected by ageing. The aN1 responses to standard stimuli were larger in amplitude in older adults than in young adults, leading to a smaller differential response between standard and deviant stimuli in older than in young adults. This result is similar to that of a recent study in which syllable changes in speech sounds were applied in the non-attentive oddball condition[31]. In our study, aP2 elicited a differential response in both groups, but a larger differential response was observed in young than in older adults, similar to earlier findings with frequency changes[34]. Again, these results indicate a weaker cortical suppression of the response to standard stimuli in older adults compared to young adults.

Unexpectedly, the groups did not differ in the aMMN amplitude although previous studies have demonstrated its attenuation in aged participants[20,21,51]. Sometimes age group differences became non-observable when short ISIs were used[52,53]. Since the MMN reflects change detection based on a comparison process between a transient memory trace formed by standard stimuli and a deviant input, the longer the applied ISI is, the more demanding the comparison process is for the brain[7]. In the current study, the ISI was relatively short, 400–500 ms, which might explain why we did not find group differences in aMMN.

When comparing the ageing-related findings between the two modalities it is notable that the somatosensory change detection, as indexed by the mismatch response, was altered in older adults while there was no such indication in the auditory modality. The somatosensory mismatch response thus seems to be more sensitive in indicating the ageing-related sensory decline than its auditory counterpart. On the other hand, in the auditory modality, ageing-related alterations were observed in response amplitudes of the N1 and P2 components that reflect stimulus encoding. For these components, increased amplitudes in older compared to young adults were found, reflecting that N1 and P2 are indicative of the altered cortical suppression in older adults. There was no evidence on ageing-related changes in the functioning of the attention shift mechanism towards stimulus changes

Characteristics	Young Mean ± SD	Older Mean ± SD	Mean Difference (95% CI)	*p*	*d*
Physical activity and fitness					
Six-minute walk test distance (*metres*, *more = better*)	—	580 ± 97			
Percent fat	—	39.3 ± 7.1			
BMI	22.5 ± 2.7	27.1 ± 4.4	4.6 (3.4 to 6.1)	0.001	1.11
Self-reported physical activity (*hrs/week*)	4.1 ± 1.1	3.1 ± 1.4			
Principal components of cognitive test scores (*rotated factor loadings*)					
Executive function	0.89 ± 0.58	0.42 ± 0.87	1.3 (1.0 to 1.6)	0.001	1.55
Error susceptibility	0.07 ± 0.61	0.03 ± 1.14	−0.1 (−0.5 to 0.3)	0.440	0.12
Explicit memory	0.62 ± 0.68	0.29 ± 0.93	0.9 (0.6 to 1.2)	0.001	0.93
Working memory	0.60 ± 0.89	0.28 ± 0.93	0.9 (0.5 to 1.2)	0.001	0.87
Cognitive test scores					
Tapping right (*clicks/10 s*, *more = better*)	53 ± 5	41 ± 5	12 (10 to 14)	0.001	2.28
Tapping left (*clicks/10 s*, *more = better*)	47 ± 5	37 ± 5	10 (8 to 12)	0.001	1.87
TMT-A (*seconds*, *less = better*)	25 ± 7	42 ± 14	17 (12 to 22)	0.001	1.29
TMT-B (*seconds*, *less = better*)	51 ± 18	96 ± 44	45 (30 to 60)	0.001	1.11
Logical memory (*points*, *more = better*)	28 ± 5	22 ± 6	6 (4 to 8)	0.001	0.97
Logical memory delayed (*points*, *more = better*)	26 ± 6	18 ± 7	8 (5 to 10)	0.001	1.08
Stroop 1 – reading (*seconds*, *faster = better*)	48 ± 7	56 ± 9	7 (4 to 11)	0.001	0.78
Stroop 2 – colour labelling (*seconds*, *less = better*)	62 ± 10	78 ± 17	16 (10 to 22)	0.001	1.00
Stroop 3 – inhibition (*seconds*, *less = better*)	91 ± 21	138 ± 35	47 (35 to 59)	0.001	1.43
Stroop 2 errors (*points*, *less = better*)	1 ± 1	1 ± 2	0.7 (0.1 to 1.3)	0.018	0.40
Stroop 3 errors (*points*, *less = better*)	1 ± 1	3 ± 5	1.9 (0.3 to 3.6)	0.012	0.44
Visual reproduction (*points*, *more = better*)	37 ± 4	34 ± 5	3 (1 to 5)	0.001	0.61
Visual reproduction delayed (*points*, *more = better*)	36 ± 4	30 ± 8	6 (3 to 8)	0.001	0.75
Digit span (*points*, *more = better*)	8 ± 2	7 ± 2	1.1 (0.4 to 1.8)	0.002	0.58
Digit span backwards (*points*, *more = better*)	7 ± 2	6 ± 2	1.2 (0.5 to 1.8)	0.001	0.66
Digit-letter (*points*, *more = better*)	12 ± 3	9 ± 3	2.4 (1.3 to 3.5)	0.001	0.79

Table 5. Sample characteristics. Difference between the age groups was tested using independent samples *t*-tests (two-tailed, bootstrap statistics). SD, standard deviation. *P*, statistical significance; *d*, Cohen's *d*.

(sP3a) in the somatosensory modality. The auditory stimuli elicited no clear P3a, and therefore ageing-related effects on P3a could not be studied.

Somatosensory, but not auditory, ERP amplitudes correlated robustly (99% CI) with cognitive performance (larger sMMR was associated with better executive functions) and physical fitness (larger sP3a was associated with longer walking distance) in older adults. A less substantial positive correlation was found between executive functions and walking distance. Thus far, no studies have investigated the relationships between ERPs elicited by somatosensory oddball stimuli and both cognition and physical fitness. However, a recent study demonstrated that sMMR is a sensitive indicator of long-term physical activity in young adults[54]. The study compared the brain activity of male twin pairs with discordant physical activity. The more active twin, who also had higher aerobic capacity and lower body fat percentage, produced a lower peak amplitude sMMR. The authors interpreted that active young adults showed better gating of deviant sensory stimuli. In the current study within the older adult group, however, better performance in the walk test was associated with higher sP3a and sMMR amplitude, but there was no correlation with ERPs that more directly reflect sensory gating, namely P50 and N80. Direct comparison of Tarkka *et al.*[54] with the current data is also hampered by the different methodology to analyse sMMR. Furthermore, P50 and N80 were not analysed in their data and thus the results concerning these components remain open.

Previous aMMN studies with older participants, which employed duration changes as stimuli, reported a correlation between the aMMN amplitude and executive functions and working memory[23,24]. In our data, aMMN to frequency deviations showed no correlations to cognitive tests in older adults. However, within the young adult group, the aMMN amplitude correlated robustly (99% CI) with working memory performance, possibly indicating that a well-functioning auditory sensory memory supports working memory. Since the age groups differed in working memory but not in aMMN, it suggests that decline in working memory functions may precede alterations of the auditory sensory memory in ageing. However, it is possible that the short ISI applied here was not the most optimal in revealing possible ageing-related alterations in the sensory memory. Additionally, aMMN showed some association (95% CI) with psychomotor speed (finger tapping test) in both age groups, alhough the results are inconclusive due to opposite direction correlations between the age groups.

Better performance in the walk test was associated with cognitive functions requiring executive control in older adults. This finding is congruent with the findings of a meta-analysis, which showed that higher physical fitness is associated with better executive functions in older adults[42]. Better performance in the six-minute walk

Sensory threshold and intensity	Young mean ± SD	Older mean ± SD	Mean difference (95% CI)	*p*	*d*
Somatosensory					
Forefinger threshold (mA)	15.8 ± 2.8	24.2 ± 6.7	8.4 (6.7 to 10.1)	0.001	1.38
Little finger threshold (mA)	15.5 ± 2.3	22.9 ± 6.1	7.3 (5.8 to 8.8)	0.001	1.33
Forefinger intensity (mA)	31.3 ± 6.0	48.3 ± 13.5	17.0 (13.5 to 20.3)	0.001	1.37
Little finger intensity (mA)	30.4 ± 5.2	45.2 ± 11.7	14.8 (11.6 to 17.6)	0.001	1.38
Auditory					
Hearing threshold right ear 1000 Hz (dB)	3.3 ± 6.2	15.9 ± 12.7	12.9 (9.7 to 16.4)	0.001	1.24
Hearing threshold right ear 500 Hz (dB)	8.2 ± 5.3	21.4 ± 13.2	13.3 (10.3 to 16.8)	0.001	1.14
Hearing threshold left ear 1000 Hz (dB)	5.1 ± 8.3	13.1 ± 11.8	10.0 (6.5 to 14.0)	0.001	0.90
Hearing threshold left ear 500 Hz (dB)	12.9 ± 6.7	23.4 ± 13.4	10.5 (7.3 to 14.6)	0.001	0.90

Table 6. Sensory thresholds and stimulus intensities. The differences between age groups were tested with independent samples *t*-tests (two-tailed, bootstrap statistics). SD, standard deviation; CI, confidence interval; *p*, statistical significance; *d*, Cohen's *d*.

test was associated with a lower body fat percentage, lower BMI, and higher self-reported physical activity levels, indicating that the six-minute walk test was a suitable objective measure of sub-maximal exercise in older adults[55].

There are some limitations to the present study. A part of the sample of older females was initially recruited for a physical exercise intervention study, which may mean these participants were on average more active than other participants of their age. However, this was balanced by recruiting about the same number of physically passive older females. Obviously, the results of the present study apply to women only. It is also worth noting that the age range in the older group (18 years) is wider than that within the young group (10 years) although most of the results remain stable after controlling the analyses for age (see Table 4). One limitation is that the somatosensory stimulus intensities were adjusted individually, but the auditory stimulus intensities were constant between the participants. Individual adjustment of the somatosensory stimulus intensities is important because it is difficult to find a fixed intensity that is not painful for someone and still discernible for all participants. Since the ERPs were measured to frequency and location changes, not to intensity changes, it might not be critical that the intensities of the auditory stimuli were of individually adjusted. Importantly, most of the results remained the same when controlling the analyses of the somatosensory brain responses for stimulus intensities and of auditory brain responses for hearing thresholds.

Due to the lack of participants' individual MRI data and suitable head models for the two relatively distant age groups, our data do not allow source analysis to compare the neural generators of the analysed brain responses between the age groups. In the grand average level, the topographies of the electrical fields of the two groups were relatively similar. Future studies should investigate whether the sources of the responses between the age groups are different.

In conclusion, ageing affects the preattentive processing of somatosensory and auditory stimuli. The sMMR indicated attenuated change detection in older adults. The long latency somatosensory brain responses were also associated with executive functions (sMMR) and physical fitness (sP3a). In the auditory modality, brain responses showed an altered encoding of sensory information in older adults, as reflected by larger standard stimulus aN1 and aP2a responses in older than young adults. Together these results suggest that ageing-related cognitive decline is observable both in cortical sensory responses and in behaviour and that physical fitness can help preserve executive functions during ageing.

Methods

Participants. Experiments were carried out in spring 2013 and summer 2014 at the University of Jyväskylä. Data were collected from 131 (41 young and 90 older) healthy females. The data of three young and nine older participants were excluded from further analyses due to contaminated electroencephalography (EEG) data or due to a lack of behavioural data or fitness assessment, resulting in the analysis of a total of 38 young and 81 older women. The ages of the young and older participants ranged from 20–30 (mean ± SD, 23.6 ± 2.8) years and 63–81 (68.1 ± 4.4) years, respectively. In terms of educational background, the percentage of young and older adults, respectively, who had completed elementary school only was 1 and 11%; 34 and 46% had completed secondary school only; 26 and 46% had completed lower tertiary school or bachelor's degrees only; and 37 and 31% had completed master's degrees or higher academic degree. All participants were right-handed and lacked any history of neurological illnesses or brain operations. The older participants were recruited from the University of the Third Age in Jyväskylä and the Society of the Retired in Jyväskylä as well as through an announcement in the local newspaper. Participants for the 2013 data collection were recruited for a larger study investigating the effectiveness of a 10-week physical exercise intervention. Here, we reported the results of their baseline measurements. For the 2014 data collection, participants who do not exercise regularly or at all were recruited for a single-day measurement. Young adult participants were recruited from the mailing lists of the University of Jyväskylä's students' association. Ethical approval for the study was obtained from the ethical committee of the Central Finland Health Care District. Written informed consent was collected from all participants, and all were given either a movie ticket or coffee package as compensation for their efforts. The experiments were undertaken in accordance with the Declaration of Helsinki.

Cognitive tests. Participants' cognitive performance was assessed with cognitive tests selected to encompass domains sensitive to cognitive ageing[2], including executive functions, perceptual speed, and verbal memory (see Supplementary Table S1). Tests were administered by a psychologist or a trained research assistant during a 60-minute session. The characteristics, including cognitive test scores, of the sample are summarised in Table 5.

Assessment of physical fitness. Three measures were used to assess physical fitness among the older adults: BMI, total body fat percentage, and a six-minute walk test[56]. Only BMI was calculated for the young adults. Participants completed all the measures during one day within two weeks of the behavioural tests and EEG experiments. BMI was calculated according to the following formula: $BMI = \frac{\text{mass (kg)}}{\text{height}^2(m)}$. Total body fat percentage was measured using dual-energy X-ray absorptiometry (DXA) (Delphi QDR series, Hologic, Bedford, MA, USA) to estimate boneless and muscleless body tissue. Participants were instructed to avoid eating just before the DXA measurement. During the scan, participants lay still on the device for approximately 10 minutes. After the DXA, the participants took part in a six-minute walk test on a 200-metre indoor track, where they were instructed to walk as far as they could for six minutes, and their heart rate was monitored after every minute. The self-reported physical activity was assessed by a five-scale question of weekly hours of medium-intensity (inducing perspiration) activity, as follows: <1, 1–2, 2–3, 3–4, and >5 hours.

Stimuli and procedure. During the EEG recording, the participant was seated in a chair in an electrically shielded, dimly lit room and monitored via a video camera. The participants were instructed to avoid all additional body movement, facial expressions, talking, and excessive head movement; to not pay any attention to any stimuli; and to be engaged in the silent movie that was played on a screen at a distance of about 1.5 metres. In both auditory and somatosensory experiments, a run of 1000 stimuli of two types varying in either location (somatosensory) or frequency (auditory) was delivered with a randomly varying stimulus onset asynchrony (SOA) of 400, 450, or 500 ms.The relatively short SOA was selected based on our earlier findings showing ageing-related changes in the amplitude of the sMMR with ISI of 500 ms[26] providing thus a solid basis for the cross modal investigation. In an oddball condition, 'standard' stimuli were frequently presented at a probability of 86%, and rare 'deviant' stimuli were presented at a probability of 14%. The somatosensory stimuli were always presented first followed by the auditory stimuli.

Somatosensory stimulation was generated with a constant current stimulator (Digitimer Ltd, model DS7A, Welwyn Garden City, UK). Electrical pulses of 200 μs were delivered via flexible metal ring electrodes moistened with conductive jelly (Technomed Europe Ltd, Maastrich, Netherlands) to the left forefinger and little finger; stimulating the cathode above the proximal phalanx and the anode above the distal phalanx. A piece of gauze was placed on the finger between the electrodes to prevent conductivity between the two electrodes in the same finger. Both fingers, forefinger and little finger, were applied standard and deviant stimuli in all participants with a counterbalanced order across the participants. Stimulus intensities were adjusted independently for each participant, and for both stimulated fingers, by double the intensity of the subjective sensory threshold. The subjective thresholds were determined by stimulating the individual fingers and asking the participants to verbally report when they sensed the stimulation. The stimulation began with very low intensities, continued with higher intensities step by step (in steps of 0.1 mA), and eventually went over the somatosensitivity threshold. The procedure was repeated three times and applied separately for both stimulated fingers. Overall, the stimulus intensities for both forefinger and little finger were greater in the older adults than in the young participants (Table 6), similar to our earlier study[26] and in line with earlier findings[57].

The auditory stimuli were sinusoidal sounds 50 ms in duration with a 10-ms onset and offset time, presented from a loudspeaker placed 90 cm above the participant, at an intensity of 75 dB (sound pressure level [SPL]) and at a frequency of either 1000 Hz or 750 Hz. Both frequencies were applied as standard and deviant stimuli in all participants in a counterbalanced order across the participants. Individual hearing thresholds for 500 and 1000 Hz separately for both ears were tested prior to the experiment with an audiometer (Mediroll SA-51, Mediroll Ltd, Debrecen, Hungary) by starting from very low intensities, going stepwise (5 dB) over the hearing threshold and lowering the intensity again well below the hearing threshold reported by the participant. This procedure was repeated three times and the lowest threshold was recorded.The hearing threshold level was generally higher among the older group than in the young group (Table 6).

Electroencephalography. The EEG was recorded using a high-impedance amplifier and the 128-channel EGI Sensor Net (Electrical Geodesics Inc., Hydrogel GSN 128, 1.0). Impedances were kept below 80 kΩ throughout the experiment. The sampling rate was 1000 Hz, and data were filtered online from 0.1 to 400 Hz. During the recording, the vertex electrode (Cz) was used as the reference electrode.

EEG data processing. Brain Vision Analyzer 2.0 software was used to analyse the data (Brain Products Gmph). Eye blinks were removed using the Gratton & Coles method[58], and channels with excessive noise and insufficient skin contact were interpolated using a spherical spline model. Offline, an average reference was applied. The electrode signals were filtered with a low cut-off of 0.1 Hz and a high cut-off of 20 Hz, both with 24 dB/octave roll-off. In addition, a 50-Hz notch filter was applied. Then, extensively large amplitude values, outside -100 to 100 μV from peak to peak, in the EEG data were rejected, and low activity periods (<0.5 μV of change within a 100-ms range) were removed. The average number of included trials (with responses to deviant and preceding standard stimuli) in the auditory experiment were 134 (min. 83, max. 150) for the older and 134 (min. 110, max. 150) for the young adults and for the somatosensory experiment 132 (min. 83, max. 150) for the older and 134 (min. 106, max. 150) for the young adults. Stimulus-locked time windows of 600 ms, from 200 ms

prior to stimulus onset to 400 ms after the stimulus onset, were extracted. A pre-stimulus onset time of 200 ms was determined as a baseline.

Although previous studies have not shown age group differences in the somatosensory oddball condition for the early components (P50, N80)[26], a visual inspection of the current data indicated potential group differences for P50 and N80. Accordingly, the maximum peak amplitudes at the C4 electrode[13] and its latency were extracted from time windows of 30–80 ms (P50) and 40–110 ms (N80) after stimulus onset.

To select the regions of interests (time windows and electrode sites) for each of the later ERP components (sMMR, sP3a, aN1, aMMN, and aP2), permutation tests[59] (4000 permutations) were performed as implemented in BESA Statistics 1.0 software (BESA GmbH) starting with all 128 electrode locations. This process was used to compare the average responses of standard and deviant stimuli in the group of young adults, which was considered a reference groups for the older adult group. The time windows were defined by first finding the time point with the highest *t*-value for each component and then using this time point as the centre of the time window. A 40-ms time window was applied for sMMR, a 50-ms window was applied for aN1 and aMMN, a 72-ms window was applied for aP2, and a 100-ms window was applied for sP3a (see Supplementary Figure S2). The width of the time window was set taking into account the latency of the differential response based on a visual inspection of the grand-averaged waveforms. The applied time windows were 153–193 ms after stimulus onset for sMMR, 258–358 ms for sP3a, 88–138 ms for aN1, 139–189 ms for aMMN, and 208–280 ms for aP2. The applied time windows based on permutation tests fitted well to the latencies of the differential responses as charged by visually observing the grand average waveforms.

The electrodes for the analysis were selected by first finding the electrode with the highest *t*-value in the middle of the each selected time window and then defining the surrounding electrodes (see Supplementary Figure S2). The activity of the electrodes within the region of interest was averaged.

The regions of interests were defined based on the data of the young adults, and the same time windows and electrode locations were used in the analysis for the older participants, since there were no substantial differences between the groups.

Statistical analysis. To compare differences in the peak amplitude and latency of somatosensory P50 and N80 between the age groups, univariate analysis of variances (ANOVA) was applied.

Due to higher sensory thresholds and thus higher stimulus intensities in the older than in the young adults, univariate analysis of covariates (ANCOVA), was also applied using stimulus intensities to forefinger and little finger as covariates. For the other ERP components, repeated measures MANOVA was used to assess differences in response amplitudes to stimulus types (standard, deviant) between the age groups separately for each response (sMMR, sP3a, aN1, aMMN, and aP2). Stimulus type (standard vs. deviant) was applied in the analysis order to investigate whether possible group differences are associated spesifically to one or both of the stimulus types (see also Fig. 8 in[60]). The mean amplitude values from the component-specific electrode pools were applied in the analysis (see Supplementary Figure S2). For these latter components, response latencies were not analysed because it was not always possible to find clear peaks for each individual and both stimulus types. The same analyses were also run with age and education as covariates.

Whenever a stimulus type × age group interaction was found, differential ERPs (deviant minus standard responses) were calculated separately for the young and older participants, and independent samples *t*-tests (two-tailed, bootstrap statistics with 1000 iterations) were performed to compare the standard and deviant responses between the groups. Effect size estimates are described as partial eta squared (η_p^2) scores for MANOVA and Cohen's *d* for *t*-tests.

A principal component analysis (PCA) was applied to reduce the dimensionality of the cognitive test scores within the whole sample. Following an exploratory analysis, an oblimin with Kaiser normalisation rotated PCA resulted in four components (eigenvalue > 1.0), including the scores from 14 cognitive tests (communalities > 0.600, $r^2 = 69.4\%$), which are listed in Table 1. The principal components (PCs) were labelled executive function, error susceptibility, explicit memory, and working memory (see Supplementary Table S3).

One-tailed Pearson's correlation coefficients and partial correlations with age and education as covariates were computed within the age groups to examine the relationships between the ERPs (deviant - standard differential response), the PC scores from the cognitive test scores, and physical fitness measures. Bootstrap statistics were performed with 1000 iterations and CIs of 99% and 95%. The threshold for statistical significance was $p < 0.05$.

Data availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author Contributions
J.M.S., P.A., and I.M.T. designed the experiment. J.M.S., V.K., T.W., S.J., S.K., and N.P. recorded and analysed the data. The interpretation of the data was performed by P.A., J.M.S., and I.M.T. The manuscript text was prepared by J.M.S. and P.A. J.S. prepared all the figures and tables. All authors reviewed the manuscript, and all the authors approved the final version of the manuscript to be published.

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Supplementary material

Automatic auditory and somatosensory brain responses in relation to cognitive abilities and physical fitness in young and older adults

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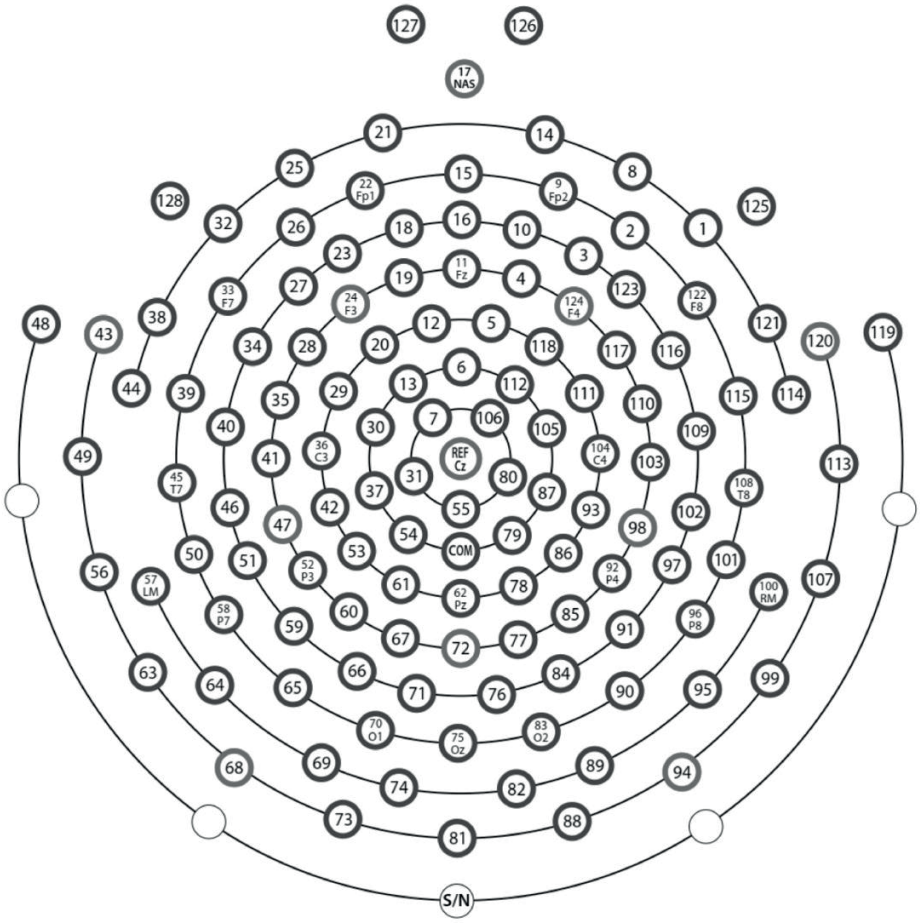
Supplementary Table S1. Cognitive tests tests and their characteristics.

Test	Reference
The Stroop Colour-Word Test is a frontal lobe task, testing executive functions. It consists of three separate A4-sheets; the first comprehends list of colour words written in black. The participant was asked to read out loud all the words. In the second sheet, there are 'Xs' printed in colour, and the participant was asked to name the ink colours. Lastly, the participant was handed a sheet with colour words printed in incongruent colours. The task was to name the colour the word was written in, prompting inhibition to read out loud the written word. All lists were instructed to be read as fast as possible, avoiding mistakes.	Alvarez, J. A. & Emory, E. (2006). Executive function and the frontal lobes: A meta-analytic review. *Neuropsychol. Rev. 16*, 17–42.
The logical memory task (WMS-R) was used to assess immediate and delayed auditory memory, and declarative memory. Participant was told a short story and the participant was asked to repeat it immediately as accurately as possible. Hereupon the recall another story was told, which was followed by its immediate recall. The participant was informed that they would be asked to recall the stories later on. In approximately one hour, in-between EEG-blocks, the participant was asked to repeat the story anew.	Elwood, R. W. (1991). The Wechsler Memory Scale-Revised: Psychometric characteristics and clinical application. *Neuropsychol. Rev. 2*, 179–201.
Visual reproduction task (WMS-R) assesses memory for nonverbal visual stimuli. It includes series of five images, where each is shown for ten seconds. After presentation, the participant was asked to draw the image from memory. In the delayed task, the participant was asked to reproduce the images in no particular order.	Elwood, R. W. (1991). The Wechsler Memory Scale-Revised: Psychometric characteristics and clinical application. *Neuropsychol. Rev. 2*, 179–201.
In the **digit span task**, the participant was told a random sequence of numbers, which were asked to repeat. If the recall was correct, the sequences eventually grew in length. Backward digit span task required the participant to repeat the told sequence in backward order, involving processing of the digits in the working memory.	Ramsay, M. C. & Reynolds, C. R. Separate digits tests: a brief history, a literature review, and a re-examination of the factor structure of the Test of Memory and Learning (TOMAL). *Neuropsychol. Rev. 5*, 151–71 (1995).
In **letter-number sequencing task** the participant was told sequences which included letters and numbers. The participant was asked to repeat the characters, first numbers in numerical order, from the smallest to the highest, and then letters in alphabetical order.	Crowe, S. F. (2000). Does the letter number sequencing task measure anything more than digit span? *Assessment 7*, 113–7.
Trail Making Test A (TMT-A) assesses basic attention. Participant was asked to connect 25 numbers in ascending order on an A4-paper without lifting the pencil. **Trail Making Test B** (TMT-B) requires divided attention. The paper included both numbers and letters. The participant was asked to connect numbers and letters by turns in ascending and alphabetical order. Both tasks were asked to complete as fast as possible, yet avoiding mistakes. TMTs assess attention and psychomotor speed. TMT-B is cognitively more demanding and it requires good executive functioning due to the simultaneous processing of two concepts.	Bowie, C. R. & Harvey, P. D. (2006). Administration and interpretation of the Trail Making Test. *Nat. Protoc. 1,* 2277–2281.
The finger tapping task was conducted in order to assess participant's psychomotor speed and motor control. In the task, the participant pressed a button on a mechanical tally counter with their thumb. The aim was to tap as many times as possible in 10 second span. The task was completed with the left hand three times consecutively, and then with the right hand. The scores for each hand were averaged across the three trials.	Ruff, R. M. & Parker, S. B. (1993). Gender- and age-specific changes in motor speed and eye-hand coordination in adults: normative values for the Finger Tapping and Grooved Pegboard Tests. *Percept. Mot. Skills 76*, 1219–1230.

Supplementary Figure S2. HydroCel Geodesic Sensor Net 128-channel electrode cap (EGI, OR, USA).



ERP component	Latency range (ms)	Electrode pool (EGI HydroCel)
sMMR	153–193	87, 104, 105, 110, 111
sP3a	258–358	7, 31, 80, 106
aN1	88–138	11, 12, 18, 19, 24
aMMN	139–189	10, 11, 16, 18
aP2	208–280	6, 105, 106, 111, 112

Supplementary Table S3. Principal component loadings rotated with oblimin with Kaiser Normalization (converged in 16 iterations) on cognitive test scores.

	Principal component			
	Executive function	Error susceptibility	Explicit memory	Working memory
Stroop1	-.83	-.209	.102	.132
TMTA	-.769	.134	-.107	.075
Stroop2	-.668	.197	.116	-.264
Stroop3	-.569	.271	-.174	-.27
TMTB	-.438	.051	-.232	-.361
Errors Stroop 2	-.015	.742	-.109	-.167
Errors Stroop 3	-.122	.664	-.209	-.033
Visual reproduction delayed	-.013	-.158	.894	.006
Visual reproduction	-.021	-.161	.874	-.118
Logical memory delayed	.157	.442	.594	.307
Logical memory	.12	.529	.53	.306
Digit span points	-.018	-.073	-.238	.923
Digit-letter	.151	-.031	.056	.745
Digit span backwards	-.106	.033	.256	.703

III

PHYSICAL ACTIVITY MITIGATES AGE-RELATED DIFFERENCES IN FRONTAL WHITE MATTER

by

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