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Effects of aging on finger movements in multiple sclerosis

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ABSTRACT

Background: People with multiple sclerosis (PwMS) report impaired hand movements and coordination. With an engineered glove we demonstrated altered finger movements in PwMS; increasing age resulted in decreased performance in healthy subjects (normative data). This study aims at investigating aging effects on finger motor performance in PwMS, in relation to disease duration and Expanded Disability Status Scale (EDSS).

Methods: Ninety-six PwMS performed repetitive finger opposition movements with the dominant hand and both hands at maximal velocity or metronome-paced. Performance was compared with the norms, and correlation coefficients between finger motor parameters, age, disease duration and EDSS were calculated.

Results: The majority of subjects was outside of the normal range according to age and probability increased with level of disability. Age significantly correlated with the glove parameters (r ranged in absolute value between 0.22–0.31; p-value in the range 0.002–0.049). Older subjects with lower disability showed worse performance than younger (p = 0.044 and 0.02), whilst younger subjects with higher disability performed similarly to older (p = 0.72 and 0.49).

Conclusion: Finger motor performance assessment provides important hints about upper limb disability, which should be evaluated in relation to age, disease duration and EDSS.

1. Introduction

Multiple sclerosis (MS) is generally considered a chronic progressive disease. The first symptoms commonly emerge between the ages of 20 and 40 years, but it should be considered that, as a result of advancements in diagnostics and treatments, many people with MS (PwMS) are living longer. Therefore, the morbidities and physiologic changes associated with the normal aging process have further effect on the severity of impairment and disability (Stern et al., 2010). Actually, older PwMS have been observed to have a faster rate of disease progression leading to irreversible disability, and this is thought to be related to progressive axonal loss. Among the main clinical manifestations of the disease we can mention sensory deficits, weakness, visual disturbances, and cognitive impairment. The normal aging process can have similar effects; therefore, the synergistic effects of age and disease constitute a real challenge to the clinician and patient, and require attention (Trojano et al., 2002; Williams et al., 1995).

Preliminary evidence for reduced physical function based on a measure of lower extremity functional performance was found among older adults with MS with respect to older adults without MS (Motl et al., 2018). A study investigating the effects of aging and MS on cognitive performance demonstrated decreased cognitive performance in older PwMS compared with older adults without the disease (Bollaert et al., 2017). Another study, based on the Multiple Sclerosis Functional Composite (Fischer et al., 1999) and the Brief International Cognitive Assessment for MS (Langdon et al., 2012), showed that the progression of motor decline is amplified by aging in MS whilst the degree of cognitive impairment does not vary across the lifespan, suggesting that older PwMS are more vulnerable to motor than cognitive disability (Roy et al., 2017).

In this context, upper limb impairment is a relevant cause of disability in PwMS, who report restrictions related to fine hand use, including coordination problems, which may impair daily living activities and thus decrease quality of life (Holper et al., 2010; Lamers et al., 2015). It should be explored how these deficits progress across the lifespan. Also, it could be very useful to quantitatively and objectively

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evaluate upper limb motor performance and assess the relationships with the disease features and with aging.

It has been demonstrated that aging has a worsening effect on hand function in healthy subjects, including lower hand strength, pinch precision, and speed (Ranganathan et al., 2001). Indeed, age-related anatomical and physiological changes negatively influence grip and pinch strength and hand dexterity in elderly (Carmeli et al., 2003).

A measure of fine hand motor function can be obtained with an engineered glove quantitatively assessing motor performance during sequences of finger opposition movements (Bove et al., 2007). With this system, we previously showed impairments in PwMS, ranging from simple tapping tasks to bimanual coordination and learning of finger motor sequences, in relation to damaged brain structures and perceived fatigue (Bonzano et al., 2017; Bonzano et al., 2013; Bonzano et al., 2014; Bonzano et al., 2008; L. Bonzano et al., 2011; L. Bonzano et al., 2011). In particular, we demonstrated that finger motor performance was altered even in PwMS with normal neurological examination (Expanded Disability Status Scale – EDSS (Kurtzke, 1983) = 0) (Bonzano et al., 2013). On the other hand, we published normative values of finger motor performance parameters obtained in 255 healthy controls (HC) stratified by age and showed that increasing age resulted in decreased performance, i.e., reduction of movement speed and of ability to coordinate bimanual movements (Signori et al., 2017).

Here, we investigated the effects of aging on finger motor performance in PwMS, taking into account disease duration and the commonly used EDSS score. To this aim, a group of PwMS performed repetitive sequences of finger opposition movements at their maximal velocity (with their dominant hand), and paced with an external cue (dominant hand and both hands simultaneously).

2. Materials and methods

2.1. Participants

We enrolled a sample of PwMS in a stable phase of the disease, without relapses or worsening greater than one point on the EDSS in the last three months. All the subjects were right-handed according to a modified Italian-translated Edinburgh Handedness Inventory (Oldfield, 1971) and naive to the specific purpose of this study.

The study was conducted according to the Declaration of Helsinki. All procedures were approved by the IRCCS Azienda Ospedaliera Universitaria San Martino—IST Ethics Committee. All participants gave written informed consent before data collection began.

2.2. Behavioral data acquisition and analysis

The included PwMS were asked to perform self-paced (with the dominant, i.e., right hand at maximal velocity) and metronome-paced (with the dominant, i.e., right hand and both hands simultaneously at 2 Hz) repetitive sequences of finger opposition movements (thumb to index-medium-ring-little fingers). An eyes-closed paradigm was chosen to exclude possible confounding effects attributable to the integration of acoustic and visual information and to prevent patients from compensating for possible sensorimotor impairments by visual inspection.

Finger motor performance was measured by means of a sensor-engineered glove on both hands (GAS, ETT S.p.A., Italy). As previously reported in details (Bonzano et al., 2013), data were acquired at 1 KHz by means of a data acquisition board (USB-1208FS, Measurement Computing, USA). An ad hoc software tool generated the acoustic pacing signal and recorded the occurrence of each tone and of the corresponding finger touch in the motor sequence. After a brief familiarization phase in which all subjects practiced the task at their own spontaneous pace and were able to perform the finger motor sequence correctly, the testing session included three randomly presented 60-s trials (one per condition).

We calculated the following parameters quantitatively assessing finger motor performance: the number of touches per second (RATE, Hz) for the dominant hand trial at maximal velocity, touch duration (TD, ms) and inter-tapping interval (ITI, ms) for the dominant hand trial at 2 Hz, and Inter Hand Interval (IHI, ms) for the bimanual trial at 2 Hz. RATE measured speed of movement, TD the duration of the contact between the thumb and another finger, ITI the time interval between two successive contacts, and IHI the absolute time interval between the corresponding touches in the two hands. According to these definitions, TD and ITI were used to describe the strategy adopted in performing the sequence of finger touches (more time spent in the contact phase than in the flight phase or vice versa), IHI was considered as index of bimanual coordination (the larger the IHI value, the more severe the impairment in bimanual coordination) (Bonzano et al., 2008). For each subject, we obtained the mean parameters values in the different conditions.

2.3. Statistical analysis

Age, EDSS and disease duration were assessed in a logistic regression model to observe their impact on the probability to have abnormal glove parameter values as compared with normative ones (Signori et al., 2017). Odds-ratio (OR) with corresponding 95% confidence interval was reported. Further quantitative characteristics were correlated by means of Spearman's coefficient and a linear regression model was performed with the glove parameters as dependent variable and age, EDSS, disease duration as independent variables. TD, ITI and IHI were log-transformed before application of the regression model. The interaction between EDSS and age was assessed into the model to test if the effect of age on the glove parameters was different according to disability levels. All characteristics with a p-value < 0.15 in univariate models were considered in the multivariate model. A p-value < 0.05 was considered statistically significant. Stata(v.14) was used for the computation. Mean with standard deviation or median with range were reported.

3. Results

Ninety-six PwMS were included in this study (67 females (69.8%) and 29 males (30.2%); age = 42.1 ± 9.5y (median = 40 y); 81 (84.4%) with relapsing–remitting disease course and 15 (15.6%) with secondary progressive disease course). EDSS ranged from 0 to 7 (median = 2.5) and disease duration from 0.6 to 44.2 y (median = 8 y).

On the basis of the normative values, the 82% ($n = 79$) of PwMS resulted to be outside of the normal range of at least one of the finger motor performance parameters in the direction of worsening.

Focusing on the single parameters, 74 (77%) PwMS were out of the normal range for IHI, 32 (33%) for RATE and 19 (20%) for TD and ITI.

Patients with higher EDSS levels showed higher probability to be out of normal range of RATE (OR = 1.51; 95% CI: 1.18–1.95; $p = 0.001$) and of TD or ITI (OR = 2.74; 95% CI: 0.94–7.96; $p = 0.064$). Further, younger subjects (OR = 0.91; 95% CI: 0.86–0.97; $p = 0.003$) and with higher disability showed higher probability to be out of range (OR = 1.43; 95% CI: 1.02–2.02; $p = 0.04$) for IHI.

All the analyzed finger motor performance parameters showed a mild but significant correlation with age: RATE ($r = -0.23$; $p = 0.021$), TD ($r = 0.31$; $p = 0.002$), ITI ($r = -0.23$; $p = 0.025$) and IHI ($r = 0.22$; $p = 0.049$), indicating finger motor performance worsening with age.

All the parameters except for ITI significantly correlated also with EDSS: RATE ($r = -0.50$; $p < 0.001$), TD ($r = 0.28$; $p = 0.006$), ITI ($r = -0.14$; $p = 0.18$) and IHI ($r = 0.34$; $p < 0.001$) indicating a relationship between finger motor performance and global disability.

Correlation with disease duration was not significant for all the parameters: RATE ($r = -0.01$; $p = 0.90$), TD ($r = 0.046$; $p = 0.66$), ITI ($r = -0.062$; $p = 0.55$) and IHI ($r = 0.066$; $p = 0.53$).

For RATE, a significant interaction between age and EDSS was observed ($p = 0.048$) (Fig. 1). In fact, in subjects with lower levels of

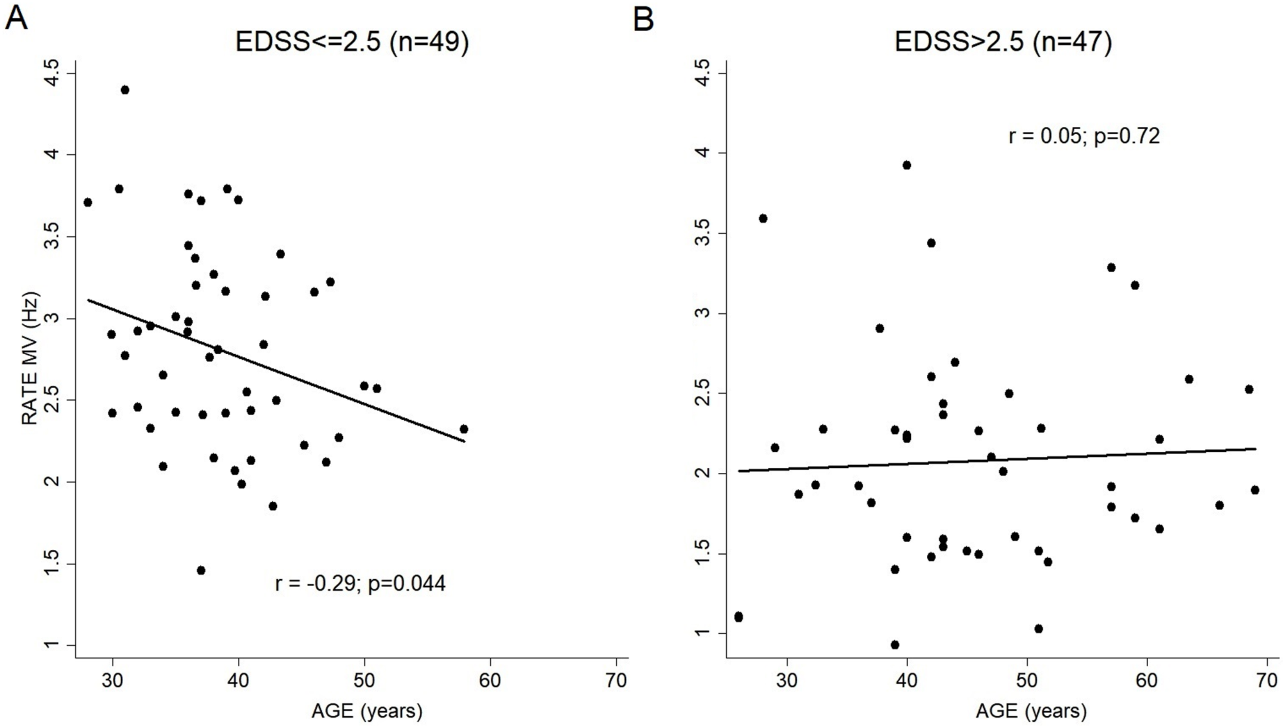

Fig. 1. Relationship between RATE (in the maximal velocity condition) and age in PwMS with lower (A) and higher (B) disability levels. EDSS was dichotomized according to the median value.

disability (EDSS < =2.5, $n = 49$ after dichotomization according to median value) age was significantly correlated with RATE ($r = -0.29$; $p = 0.044$), whilst in subjects with higher disability (EDSS > 2.5, $n = 47$) the correlation was very low ($r = 0.05$; $p = 0.72$).

For TD, in multivariate analysis interaction between age and EDSS ($p = 0.046$) was significant. In particular, an increase in TD with age ($r = 0.34$, $p = 0.02$) was observed among PwMS with lower disability whilst this was not observed among PwMS with higher disability ($r = 0.11$; $p = 0.49$) (Fig. 2).

For ITI, in multivariate analysis both EDSS ($p = 0.70$) and its interaction with age were not significant ($p = 0.61$). Only age was significantly related to ITI, as calculated by correlation (Fig. 3).

Concerning bimanual coordination impairment (IHI), at multivariate analysis no interaction was detected between age and EDSS ($p = 0.73$); in the multivariate model only the association with EDSS was retained as statistically significant (Fig. 4; $p < 0.001$), while the correlation with age was lost ($p = 0.18$).

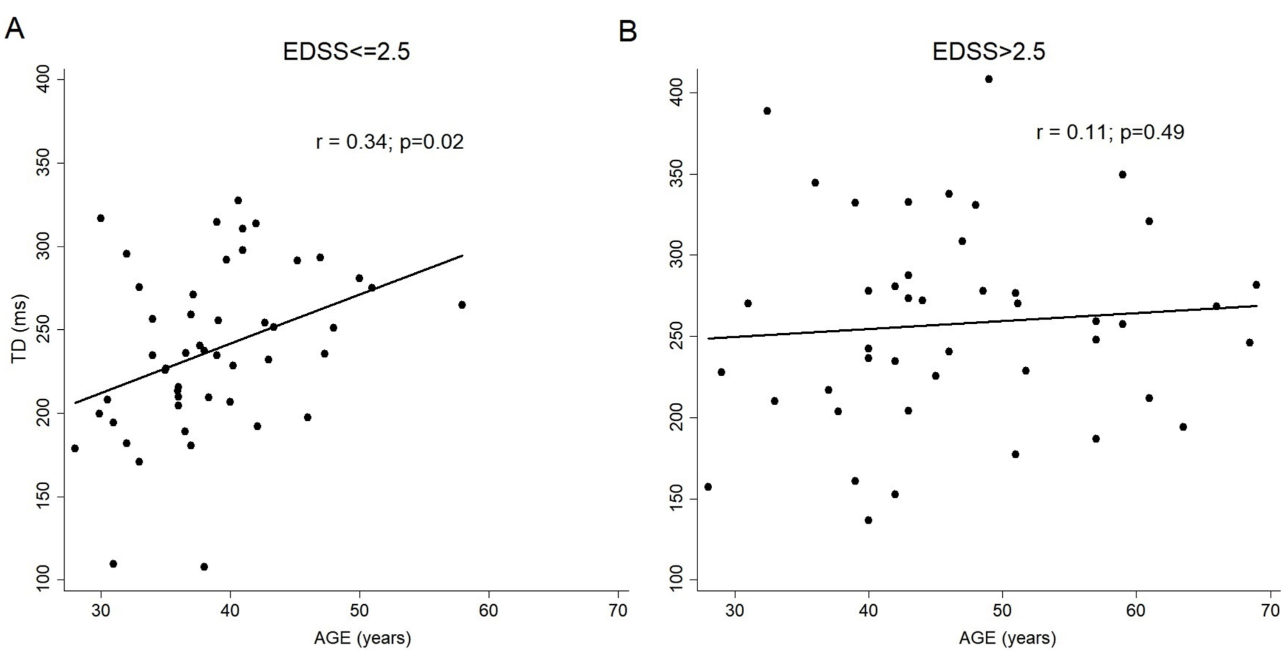

Fig. 2. Relationship between touch duration (TD) and age in PwMS with lower (A) and higher (B) disability levels. EDSS was dichotomized according to the median value.

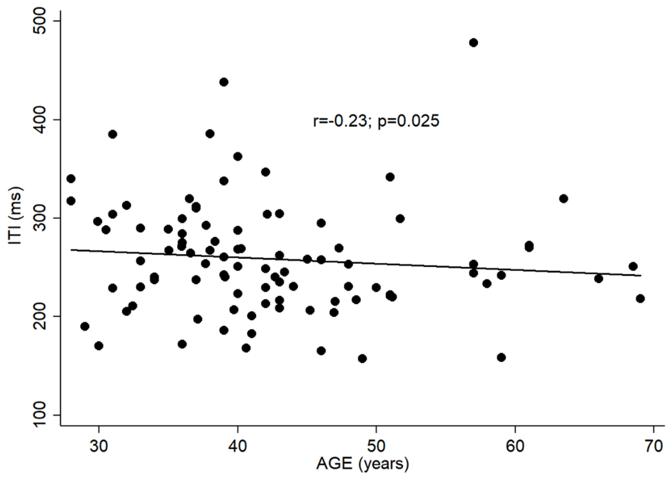

Fig. 3. Relationship between inter-tapping interval (ITI) and age.

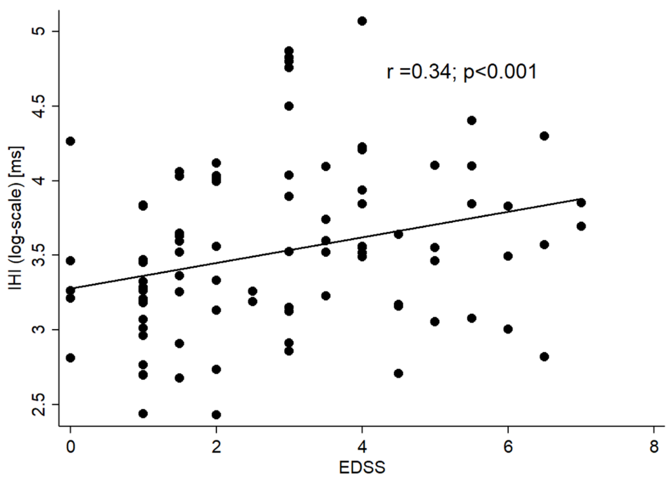

Fig. 4. Relationship between inter-hand interval (IHI) and EDSS.

4. Discussion

In this work, PwMS showed finger motor performance worsening with aging. When analyzing the present data with respect to the normative data according to age, PwMS mostly showed bimanual coordination impairment, followed by movement slowing and then by a change in the adopted strategy (finger contact vs. inter-tapping interval).

Specifically, with increasing age we found a reduction in movement speed and an increase in touch duration (together with a decrease in the time interval between two successive contacts) and inter-hand interval (i.e., bimanual coordination impairment). A relationship of age with RATE and IHI was previously found in healthy subjects (Signori et al., 2017), whilst the performance worsening represented by TD and ITI for older subjects was a new result in PWMS.

As already underlined in our work reporting normative data, there is scientific evidence showing an overall age-related performance decline due to movement slowing (Birren and Fisher, 1995; Krampe, 2002), increased movement variability (Christou, 2011), and multi-joint and interlimb coordination difficulties (Seidler et al., 2002; Solesio-Jofre et al., 2014). It should be considered that properties of human brain tissue change across the lifespan, with multiple biological processes driving changes in the white matter (Yeatman et al., 2014). Particularly, the decline in bimanual coordination was related to a decrease in microstructural integrity along the corpus callosum, as demonstrated in PwMS (Bonzano et al., 2008; Eliassen et al., 2000); on the other hand, age-related declines were shown in callosal size and integrity and considered to have a role in unimanual and bimanual control deficits (Fling et al., 2011). In PwMS this aspect assumes even more importance, as the corpus callosum is commonly affected (Evangelou et al., 2000).

In addition, PwMS showed a change in finger motor performance strategy with aging, increasing the time of the contact between the thumb and another finger, and this could be due to sensorimotor integration deficits and reduced transmission of sensory information to be used for motor planning. This is in line with a study based on reaction time tasks, suggesting defective sensorimotor integration mechanisms in MS (Cabib et al., 2015).

Also, it is known that the EDSS is mainly based on lower limbs impairments, therefore it is not strictly related to the parameters measured by the glove system; however, general disability was found to be partly related to finger motor performance. Here, we demonstrated a difference in the relationship between age and the glove parameters in different sub-groups with different levels of disability. Indeed, older subjects with lower disability measured by the EDSS showed worse performance than younger, whilst younger subjects with higher disability performed similarly to older. In other words, for subjects with lower disability age had great influence on finger motor performance, while in subjects with higher disability the effect of aging was reduced in the sense that the accumulated disability counted more than age.

In conclusion, this study demonstrates that PwMS undergo performance changes associated with MS and its progression, as well as those associated with normal aging.

Understanding how MS manifests across the lifespan could have important implications for tailoring assessment and treatment. Finger motor performance measurement provides important hints about upper limb disability, which should be evaluated in relation to age (i.e., comparison with normative data on healthy subjects), disease duration and EDSS. The weight of age in contributing to finger motor performance could be particularly relevant in subjects with primary progressive MS, generally characterized by older age and mild disability at the onset of the disease.

We might suggest that the first aspect to be impaired is bimanual coordination, followed by movement slowing and then a change in the adopted strategy, which becomes more based on the phase of finger contact in which sensory information is integrated to plan the subsequent movement in the sequence.

Here, we limited our study to the analysis of cross-sectional cohorts of PwMS across the lifespan to shed light on aging effects on finger motor performance in MS. Long-term longitudinal studies should be required to more properly investigate the aging effects and the manifestation of different aspects of hand disability in PwMS during the disease course, identifying the weight of different factors influencing performance.

Declaration of Competing Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

Maria Pia Sormani has received consulting fees from Biogen, TEVA, Merck, Roche, Novartis, Sanofi Genzyme, Medday, GeNeuro

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