Acknowledgement

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Additionally, we would like to thank other researchers at the faculty of movement and rehabilitation sciences (building De Nayer, KU Leuven) for guiding the research project in the right direction. We also want to thank our fellow students, friends and family members for their support and encouragement during this master thesis.

Finally, we are grateful to each other for the work we have done and the pleasant cooperation. Although we did not know each other at first, we were able to work well together quickly and support each other with help and advice when needed.

Maasmechelen-Mol, 05-06-2018 K.Q.-S.V.

Research context

This paper was written in the context of our master thesis. It is a duo-master thesis and it is the final piece of our five-year degree in Rehabilitation Sciences and Physiotherapy at Hasselt University. The thesis was started in September 2016 and ran over two years. In the first year, we completed a literature review about the influence of aging on the inhibitory system during a motor task. From the start, we had the privilege to be part of an ongoing cooperation between the REVAL institute at UHasselt and at the motor control laboratory at KU Leuven. Therefore, it was possible for us to participate in a research project about the role of GABA concentration and modulation in motor related areas in the aging brain. This research was conducted under the direction of our promotor Dr. Koen Cuypers. In the second year, we wrote this paper based on data of this research project.

For the entire research, healthy young adults were compared to elderly for detection of age-related changes in the brain. Brain structure [assessed by Magnetic Resonance Imaging (MRI)], neurometabolites [assessed by Magnetic Resonance Spectroscopy (MRS)] and cortical excitability [assessed by Transcranial Magnetic Stimulation (TMS)] were of interest. For our master thesis, the focus was only on the TMS measurements. We participated in the data collection by holding the TMS coil to the optimal stimulation spot (hotspot). This was done with the help and under supervision of our promotor. This innovative study about TMS will examine intra- and interhemispheric interactions during fixed timings in the preparation and the action selection period of a motor task in a group of young adults and a group of healthy elderly. After data-processing, it became clear that the analysis of all this data would be too ambitious for us as students. Because of this, we decided in consultation with our promoter to formulate our own research question for our thesis. We chose to only focus on the intrahemispheric GABAergic inhibition. Therefore, we posed the following research question: 'Is there a difference in modulation of SICI during the preparation and action selection period of a choice reaction task between young adults and elderly?'

Because we participated in an ongoing project, subjects were already recruited and the research design was worked out for us. Both master students were involved in the project's data collection that took place between November 2016 and March 2017. More specifically,

we helped with conducting the TMS experiments in the lab on a daily basis for about ten weeks. Additionally, we helped with a part of the data-preprocessing. This preprocessing consisted of visual inspection and preparing the data (adapt naming, etc.) for further analysis. Both master students performed statistical analysis of the results, except for the execution of two linear mixed models. Linear mixed models were only limitedly discussed in our educational program. To carry out this analysis, another statistical program had to be used. Our knowledge turned out not to be extensive enough to carry out this analysis ourselves. However, we have run through this statistical analysis with our promoter so we understand how the analysis was done. This paper, including acknowledgement, research context, abstract, introduction, method, results and discussion was written by ourselves.

This research fits within the field of neurological rehabilitation, and was conducted at the faculty of motion and rehabilitation sciences, building De Nayer, Tervuursevest 101, 3001 Leuven. For this duo-master thesis, equal contribution until the final product was delivered by both master students.

Age-related changes in intrahemispherical interactions within motor areas of the brain.

Is there a difference in modulation of SICI during the preparation and action selection period of a choice reaction task between young adults and elderly?

Abstract

Background: Several studies examined the effects of intracortical inhibition during a motor task but the evidence between younger adults and elderly is limited.

Objectives: The aim of our experiment is to explore the influence of aging on the intracortical inhibitory system during a motor reaction task in healthy subjects measured by TMS.

Participants: Fifty-three subjects were recruited by advertising in public places in and around Leuven and were divided into two groups based on age. The first group of aged between 18-30 (n=25) and the second group were the elderly of 65-77 years old (n=28).

Measurements: Subjects had to perform a choice reaction task (CRT), which required different responses of right and left index finger. Short-interval intracortical inhibition (SICI) was used to measure intracortical inhibition. Timing of TMS pulses were semi-randomized at three different timings during the experiment, in the preparation period at the warning signal (WS) or the imperative signal (IS), and in the action selection period at 75% of the EMG activity onset.

Results: During the preparation period, a significant GROUP effect ($p=0.037$) and significant GROUP x TARGET HEMI ($p=0.028$) interaction was found. More specific, older adults showed less inhibition during the preparation period. Furthermore, in the left hemisphere elderly showed a significant release of inhibition as compared to the young group. During the action selection period, a significant REQUIRED ACTION effect ($p<0.001$) and significant TARGET HEMI x REQUIRED ACTION ($p=0.026$) interaction was found. For the left hemisphere, more inhibition occurred during no response compared with right response. For the right hemisphere, more inhibition occurred during no response compared with both or left response. So, no difference of age was found during the action selection period.

Conclusion: There is a difference in modulation of SICI during the preparation between younger adults and elderly but not during the action selection period of a choice reaction task.

Introduction

Elderly are less independent with respect to activities of daily living because of motor impairments caused by the aging process, this may lead to reduced quality of life (Scherder, Dekker, & Eggermont, 2008). Therefore, it is important to have an insight about how the aging process influences function within the motor system. It is known that within the primary motor cortex (M1), age-related changes in inhibitory neurotransmission mediated by γ-aminobutyric acid (GABA) may influence motor impairments (Levin, Fujiyama, Boisgontier, Swinnen, & Summers, 2014). GABA is the most important inhibitory neurotransmitter in the nervous system (Leonard, 2002).

Transcranial magnetic stimulation (TMS) is now an increasingly used measurement tool that can be used to make a link between inhibitory functions and motor impairments in elderly. With TMS, magnetic pulses can be applied over the skull. This technique is non-invasive and not painful (Barker, Jalinous, & Freeston, 1985).

TMS can be applied as single-pulse TMS (sTMS), paired-pulse TMS (ppTMS) or repetitively TMS (rTMS) (Chen & Petrescu, 2012). Brain functioning is investigated with sTMS and ppTMS whereas rTMS is used to modulate brain activity for a period that can last beyond the stimulation duration (Klomjai, Katz, & Lackmy-Vallee, 2015). The excitability of the corticospinal tract can be assessed with sTMS and corticocortical connections can be determined by ppTMS (Vahabzadeh-Hagh, 2014).

Paired-pulse TMS is divided into dual site TMS (dsTMS) and double pulse TMS (dTMS). With dsTMS, interhemispheric inhibition (IHI) between primary motor areas (M1's) can be examined by delivering a CS in the motor cortex, which causes inhibition of the opposite motor cortex MEP delivered by the TS (Ferbert et al., 1992). With double pulse TMS (dTMS), intrahemispherical interactions can be examined locally within the motor cortex by delivering two TMS pulses through the same coil (Turchick, 2015). A subthreshold conditioning stimulus (CS) at interstimulus interval (ISI) of 1-5ms prior to a suprathreshold test stimulus (TS) can elicit a reduction of the test motor evoked potential (MEP), which causes an inhibition of the motor cortex (Kujirai et al., 1993). This process is called short latency intracortical inhibition

(SICI) and is mediated through activation of post-synaptic GABAa receptors (Ziemann, Lonnecker, Steinhoff, & Paulus, 1996).

Several studies examined the effects of intracortical inhibition during a motor task and a few explored the effects between younger adults and elderly. In a rest condition, findings are inconclusive. Moreover, Opie and Semmler (2014) reported no difference in SICI was seen between young adults and elderly. In contrast, two studies showed a decrease of SICI in rest with increasing age (Heise et al., 2013; Marneweck, Loftus, & Hammond, 2011). During the preparation period prior to action, inhibition occurred to prevent premature responses (Sinclair & Hammond, 2008). SICI decreased towards movement onset in the preparation period (Heise et al., 2013). Overall, SICI was reduced during contraction (Sharples & Kalmar, 2012), and more decrease of SICI was seen in elderly compared with young adults (Opie & Semmler, 2014).

Because evidence of differences in intracortical inhibition between younger adults and elderly is still limited, the aim of our experiment is to explore the influence of aging on the intracortical inhibitory system during a motor reaction task in healthy subjects measured by TMS. Therefore, our research question is: 'Is there a difference in modulation of SICI during the preparation and action selection period of a choice reaction task between young adults and elderly?'. Here, we hypothesize that there will be age-related differences, more specific we expect less modulation potential of SICI in elderly as compared to young adults.

Method

Participants

Fifty-three subjects were recruited by advertising in public places in and around Leuven. They were admitted to the study if they met the in- and exclusion criteria. Inclusion criteria were: healthy subjects, age between 18-30 or 65-77 years old, normal or corrected to normal vision and right handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Exclusion criteria were: no management of Dutch or English language, a medical condition that affects the upper extremity, neurological or psychiatric condition, the use of psychoactive medications and medical history that limits TMS (assigned by TMS screening list). These subjects were divided into two groups based on age. The first group of adults aged between 18-30 (n=25) and the second group were the elderly of 65-77 years old (n=28). The protocol was approved by the committee on Medical Ethics of the UZ Leuven on 04/11/2016, in accordance with the declaration of Helsinki. The informed consent was signed by each subject before the start of the experiment.

Procedures

Each subject underwent two TMS sessions that were carried-out on different days. Both sessions took about three hours each and included preparation time, assessing the reaction time and the eventual experiment with TMS measurements. The experiment was part of a bigger experiment where in each session one interhemispheric interaction [dorsal premotor cortex (PMd) to contralateral primary motor cortex (M1) or M1 to contralateral M1] was conducted in both directions (left to right hemisphere and vice versa) and one intrahemispheric interaction (within left or right M1). For our research question, we are only interested in the intrahemispheric interactions. Primary outcome measures were motor evoked potentials (MEPs) and EMG reaction time of left and right first dorsal interosseous (FDI).

Preparation

The subjects were welcomed at the entrance of building De Nayer on the appointed time and escorted to the lab. Here, the subject took a seat at a table where the experiment was

conducted. The subject was asked to take off jacket/watch/jewelry/hearing aid. The subject was asked to read the informed consent and sign if agreed. In addition, the subject completed the Edinburgh Handedness Inventory (Oldfield, 1971) and a screening list for contraindication for TMS. The researcher asked if everything was clear and, if necessary, provided additional information.

Electrodes were placed on the right- and left FDI for continuous EMG measurement. Grounding electrodes were placed on the processus styloideus ulnae left and right. Electromyographic signals from the FDI muscle were continuously monitored and measured using EMG (Bagnoli-16, DelsysInc, Boston, USA). After amplification (gain = 1000), band pass filtering (2–2000 Hz) and 50/60 Hz noise elimination (Humbug, Quest Scientific, North Vancouver, Canada) the recorded EMG signals were digitized at 5000 Hz (CED Signal Version 4.03, Cambridge Electronic Design, Cambridge, UK) and were stored on a laboratory computer for offline analysis.

A swimming cap was placed on the head and covered with paper tape to draw on later. The vertex was determined as the crossing point of both middle of the distance of nasion to inion and from ear to ear. Based on the vertex location, a one by one cm grid was drawn on the cap.

Single-pulse TMS was used to determine some important variables. Magnetic stimuli (Magstim BiStim2, Whitland, South West Wales, UK) were delivered using a 50-mm loop-diameter figure of-eight coil. TMS was applied on the scalp with the coil rotated 45° away from the midsagittal line (Brasil-Neto et al., 1992; Mills, Boniface, & Schubert, 1992). In both hemispheres, a suprathreshold intensity was used to search for the point for optimal stimulation of the motor cortex (hotspot). This starting location for finding the hotspot was always fixed at location 1/5 (1 cm frontal to the vertex and 5 cm lateral). To determine the search intensity, we started with an intensity of 30% and turned it systematically up with 5% until consistent motor evoked potentials (MEPs) of the FDI occurred. A MEP was defined as the signal evoked by TMS with an amplitude greater than 50 µV in a relaxed muscle (EMG value FDI < 5µV). During the preparation, a computer was placed in front of the subject to provide biofeedback on his EMG signal.

Once this intensity was determined, the left and right hotpot was searched with aid of the grid. The hotspot is defined as the point that achieves the highest average MEP on consistent basis. To find the hotspot in a standardized manner, series of five pulses were administered at location 1/5 and at surrounding location until the 'best' location (hotspot) was found. Both hotspots were marked on the swimming cap. The coil position and orientation at the hotspot was co-registered to the individual anatomical MRI images using an MRI-based neuronavigation system (Brainsight, Rogue Research Inc, Montreal, Quebec, Canada).

Finally, rest motor threshold (rMT) and one millivolt intensity (1mV) were determined at the hotspots. For the rMT, the lowest intensity which still achieved at least 5 to 10 MEPs was searched (Rossini et al., 1994). The 1 mV intensity was defined as the intensity that evoked a MEP with an amplitude of approximately 1mV peak-to-peak in relaxed FDI (Nardone et al., 2016).

Performing the reaction task

Subjects were seated in a comfortable chair with both feet in contact with the floor. Their forearms were pronated leaning on the board on which the task was performed (see Fig. 1). This board consists of two pairs of micro switches. On the right home button the subject placed their right index finger and the same was done on the left. The two target buttons are placed medial, inferior and perpendicular relative to the home buttons, so they can register an abduction movement.

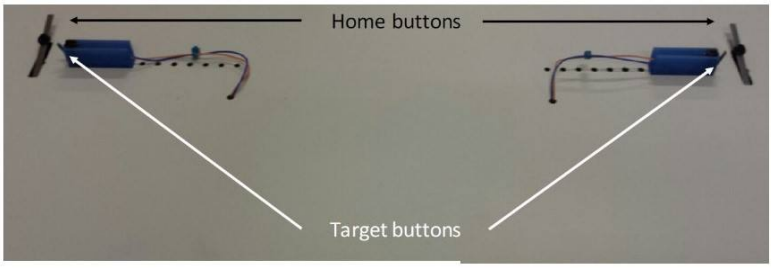

Figure 1: the board for task performance

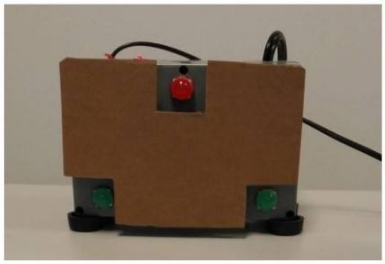

Figure 2: the signaling box

A foam was placed under their elbows to make the setup more comfortable. One meter in front of the subject, a signaling box was placed (see Fig. 2). The box consists of a red light on top and two green lights in the right and left lower corner respectively. This instrument gave the subject instructions for the choice reaction task (CRT).

The CRT task is a motor task where the subject had to react by an abduction and reposition movement of the index finger. Instructions were given by the signaling box. A warning signal (WS) with duration of 500ms was given at the start of each trial by displaying a red light. After this, an imperative signal (IS) with a duration of 1s could be given by the lit-up of one or two green lights. More specific, there were four possible conditions: left green light turned on (left response), right green light turned on (right response), both green lights turned on (bimanual response) or no lights were turned on (no response). These conditions were semi-randomized during the experiment. Between trials (between WS) time varied between 4 to 6s.

Prior to the start of the main experiment, EMG reaction time of the subject was determined. This was defined as the time from the IS to EMG onset of the FDI. EMG onset was visually determined in the EMG signal. For this, the subject took a practice run of 40 trials. Only in the first session, this was preceded by an extra practice run for familiarization with the task.

The experiment

SICI was used to measure intracortical inhibition. The ISI was set at 3 ms for the measurement of direct inhibition by the GABAa system (Ziemann et al., 1996). CS was given at 80% rMT (Ziemann et al., 1996) and test stimulus at 1 mV intensity (Heise et al., 2013). Magnetic stimuli were delivered by two connected Magstim 200² units. Timing of TMS pulses were semi-randomized at three different timings during the experiment. These single and double pulses were applied in the preparation period at the WS or the IS, and in the action selection period at 75% of the EMG activity onset (see Fig. 3).

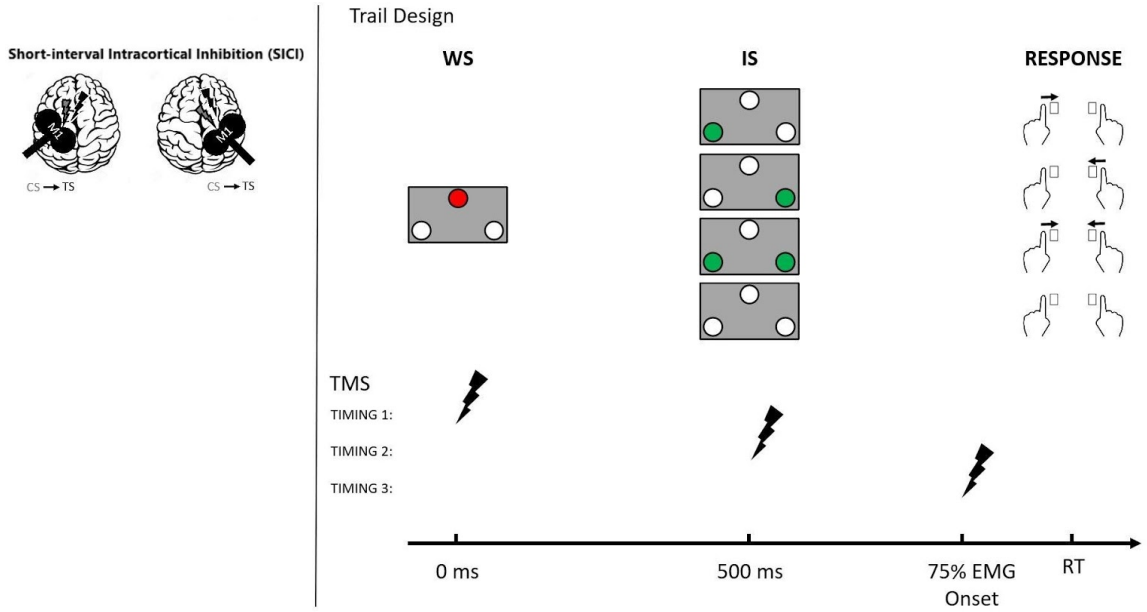

Figure 3: Timing of TMS pulses at three different timings during the experiment. These pulses were applied in the preparation period at WS or IS, and action selection period at 75% of the EMG activity onset.

SICI was divided per hemisphere, each consisted of three block measurements. A block consisted of 54 trials. All together, this resulted in 324 trials SICI per subject (see Fig. 4). Below, the structure of a block design will be explained (see Fig. 5).

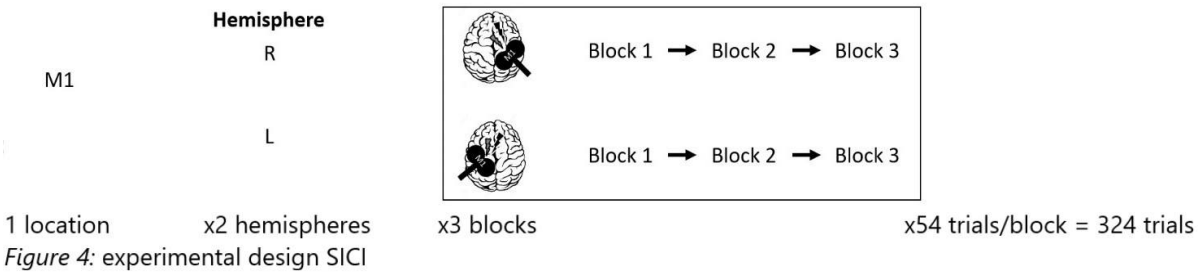

Figure 4: experimental design SICI

During WS, a total of 4 single pulses and 4 double pulses were given, each followed by a different response: R move, L move, L and R move, no response. Here, the excitability is measured before the subject knows which response will be expected. Because at this timing the subject is still unaware of the expected response, the MEPs resulting from stimulation at these timings were merged and considered as the same condition. More specific, this allows the 4 SP to be seen as 1 condition and the 4 DP as another one. The same distribution of pulses was used for the IS. At 75% of the EMG activity onset, the subjects knew the required response. So, we suspected that the excitability would be different for each response. In our design, we want to make sure that each condition consisted of 4 pulses per block. To ensure

this, each response had to be repeated 4 times for the SP and the DP. Beside these pulses, 6 trials were without TMS to measure the reaction time of the different responses. These trials were important as it is reported that TMS administered prior to a response has an influence on the reaction time (Pascual-Leone, Houser, Grafman, & Hallett, 1992). By this block design we could realize a total of 12 pulses per condition per hemisphere over the 3 blocks, except for the conditions without TMS.

Block Design

Condition	TMS timing	Single/Double Pulse	Required Response	Repetitions per block
1	WS	SP	L	1
2	WS	SP	R	1
3	WS	SP	L+R	1
4	WS	SP	no response	1
5	WS	DP	L	1
6	WS	DP	R	1
7	WS	DP	L+R	1
8	WS	DP	no response	1
9	IS	SP	L	1
10	IS	SP	R	1
11	IS	SP	L+R	1
12	IS	SP	no response	1
13	IS	DP	L	1
14	IS	DP	R	1
15	IS	DP	L+R	1
16	IS	DP	no response	1
17	75%EMG	SP	L	4
18	75%EMG	SP	R	4
19	75%EMG	SP	L+R	4
20	75%EMG	SP	no response	4
21	75%EMG	DP	L	4
22	75%EMG	DP	R	4
23	75%EMG	DP	L+R	4
24	75%EMG	DP	no response	4
25	noTMS	noTMS	L	2
26	noTMS	noTMS	R	2
27	noTMS	noTMS	L+R	2

54 trials/ block

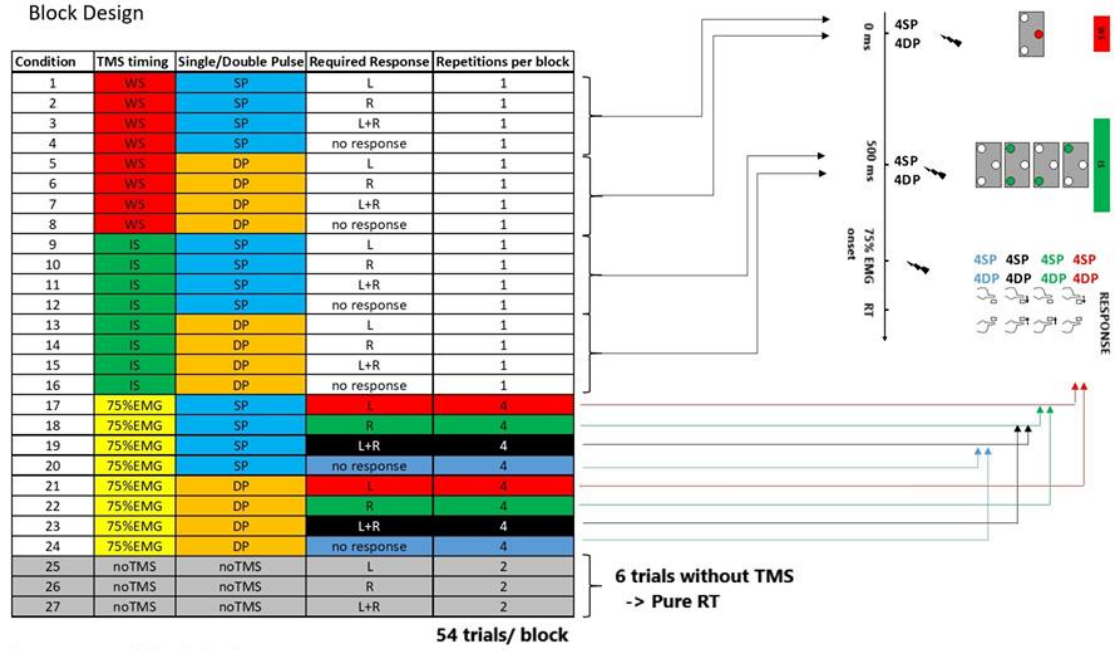

Figure 5: SICI block design

Data analysis

Data collection happened by trial using Signal (v 4.03) software. Timing of this data collection started 100ms before the WS and lasted for 1.5s after the IS. Signal configuration files were exported to a txt-file in the subject directory and in the corresponding folder. Offline semi-automatized data-analysis was done with Matlab R2016b (MATLAB R2016b, The MathWorks Inc., Natick, MA, 2000). Matlab finally outputs an excel-file with data for each subject. The raw data was sorted and from this, trials were excluded when (1) index fingers were not placed on the home buttons prior the WS, (2) the wrong response was generated, (3) EMG signal of the FDI was more than 20µV during the TMS measurement (Cuypers et al., 2013) (4) EMG signal, resulting from voluntary muscle activity, was present during the TMS pulse and (5) artifacts were seen in the data. The errors were stored in an excel-file and the corresponding data was excluded from analysis. For SICI, the MEPs were normalized to its corresponding single pulse

value, to have the net-inhibition/facilitation effect independent of the fluctuation of the excitability throughout the experiment.

The R-language LmerTest package (v.3.3.2.) was used for data analysis. The analysis was performed under supervision of CENSTAT. The significance level was set at alpha = 0.05. Two separate linear mixed models were used, one for the preparation period and one for the action selection period. In both, SUBJECT acted as the random factor. GROUP (young/old), TARGET HEMI (left/right hemisphere) and PULSE TIMING (WS/IS) were the fixed factors for the preparation period. GROUP (young/old), TARGET HEMI (left/right hemisphere) and REQUIRED ACTION (left/right/both/no move) were the fixed factors for the action selection period. In both models, interaction between all fixed factors were included by three 2-way interactions and one 3-way interaction. The QQ plot was used to check for normality. In both models, a transformation was needed to meet the normality assumption. Transformations were based on Box-Cox to determine which transformation was most appropriate (Box & Cox, 1964). In the preparation period, Lambda derived from the Box-Cox was close to zero, suggesting that the most optimal transformation was a log transformation. In the action selection period, a box-cox transformation with Lambda 0.127 was used ($Y= (Y^{\lambda}-1)/\lambda$). After this, the models where refined step by step and Post-hoc pairwise comparison was used by Tukey contrasts.

Results

Subject characteristics

From the 53 included participants, three participants were excluded because the stimulation intensity was too high to ensure safety. This resulted in 25 younger adults and 25 elderly participants. As expected, a significant difference between both groups was found for age. Oldfield scores also revealed to be significantly different between both groups, however according to the Oldfield categories, all subjects were considered as right-handed (Oldfield, 1971) (Table 1).

Table 1. Subject characteristics presented as mean (SD)

	Young (n=25)	**Old (n=25)**	**p-value***
Age (years)	22.08 (4.04)	67.48 (4.37)	<0.0001
Oldfield	87.64 (13.92)	94.43 (10.15)	<0.0001

* statistically significant difference (p-value < 0.05)

TMS parameters

Both groups were found to be homogenous for conditioning stimulus and test stimulus in the left (Table 2) and right hemisphere (Table 3).

Table 2. SICI left TMS parameters presented as mean (SD)

	Young (n=25)	**Old (n=25)**	**p-value***
CS	41.76 (6.54)	42.56 (8.39)	0.7086
TS	66.52 (10.72)	67.88 (12.00)	0.6744

* statistically significant difference (p-value < 0.05)

Table 3. SICI right TMS parameters presented as mean (SD)

	Young (n=25)	Old (n=25)	p-value*
CS	42.64 (6.75)	44.28 (8.16)	0.4426
TS	67.48 (11.26)	68.28 (11.63)	0.8059

* statistically significant difference (p-value < 0.05)

Intrahemispheric inhibition - SICI

Preparation period

After the model was refined, a significant GROUP effect (p=0.037) and significant GROUP x TARGET HEMI (p=0.028) interaction was found. Tukey contrasts revealed one significant contrast, namely an increase in inhibition in the left hemisphere for the young subjects in contrast to the older (p=0.017) (see Fig. 6). More specific, older adults showed less inhibition during the preparation period.

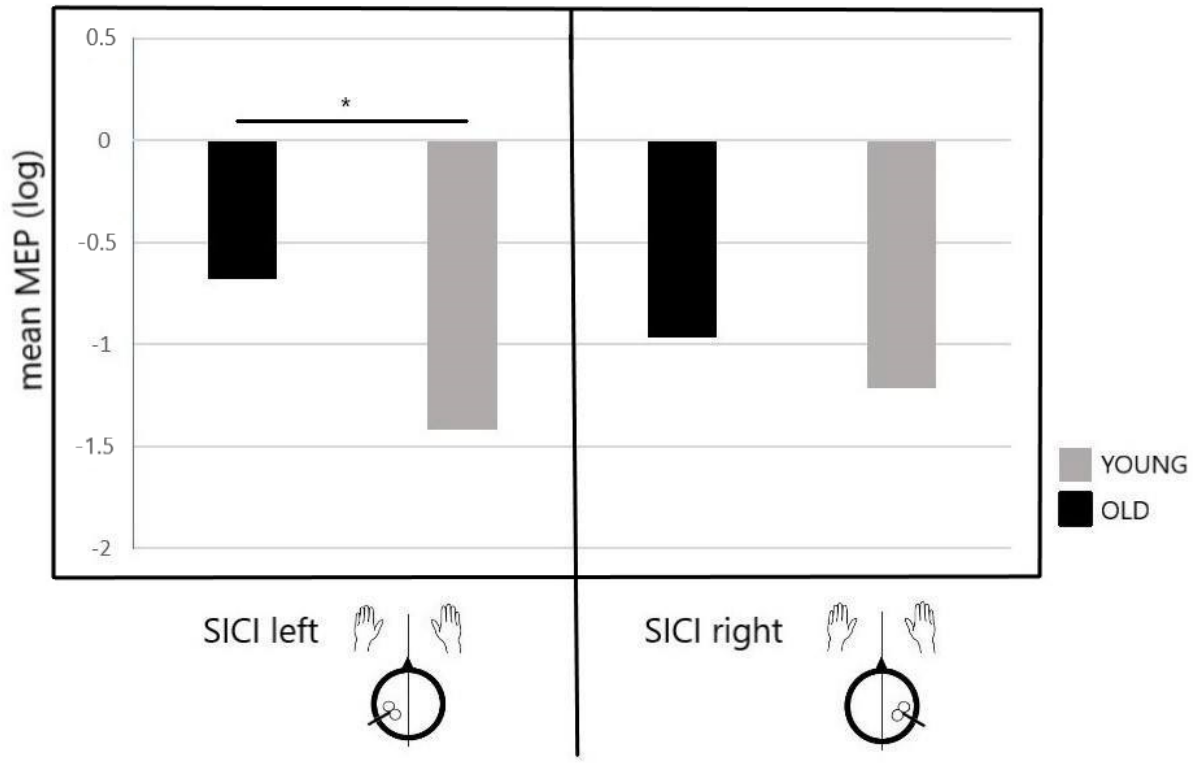

Figure 6: preparation period *p<0.05

Action selection period

After the model was refined, a significant REQUIRED ACTION effect ($p<0.001$) and significant TARGET HEMI x REQUIRED ACTION ($p=0.026$) interaction was found. In the left hemisphere, Tukey contrasts revealed a significant difference between no response and right response ($p=0.020$) (see Fig 7.). For the right hemisphere, Tukey contrasts showed a significant difference between no response and left response ($p=0.036$) and between no response and both ($p=0.025$) (see Fig. 8).

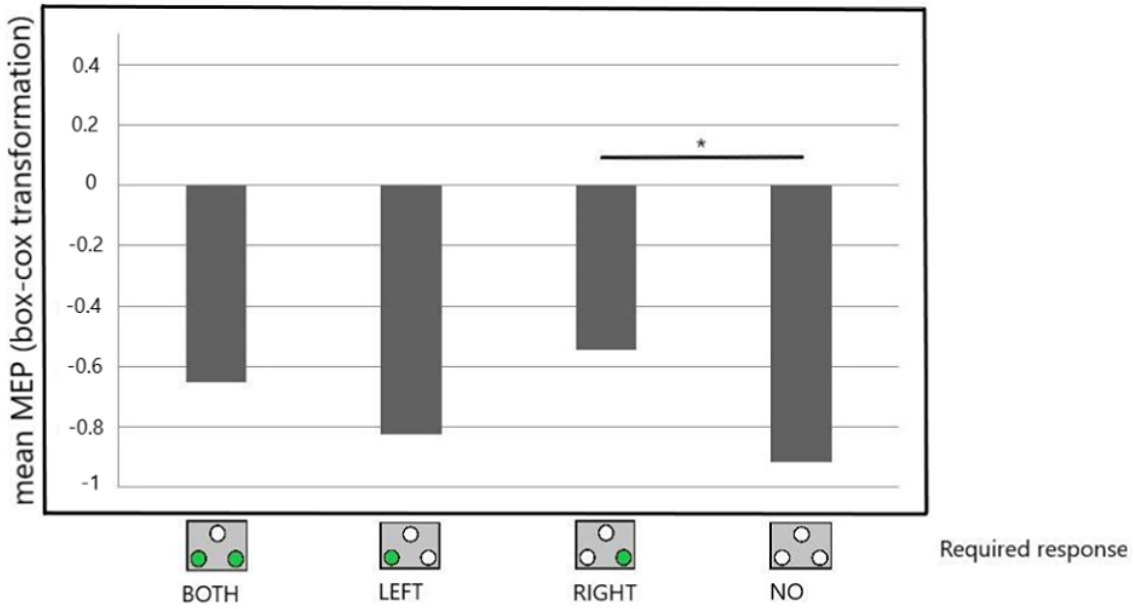

Figure 7: action selection period left hemisphere *p<0.05

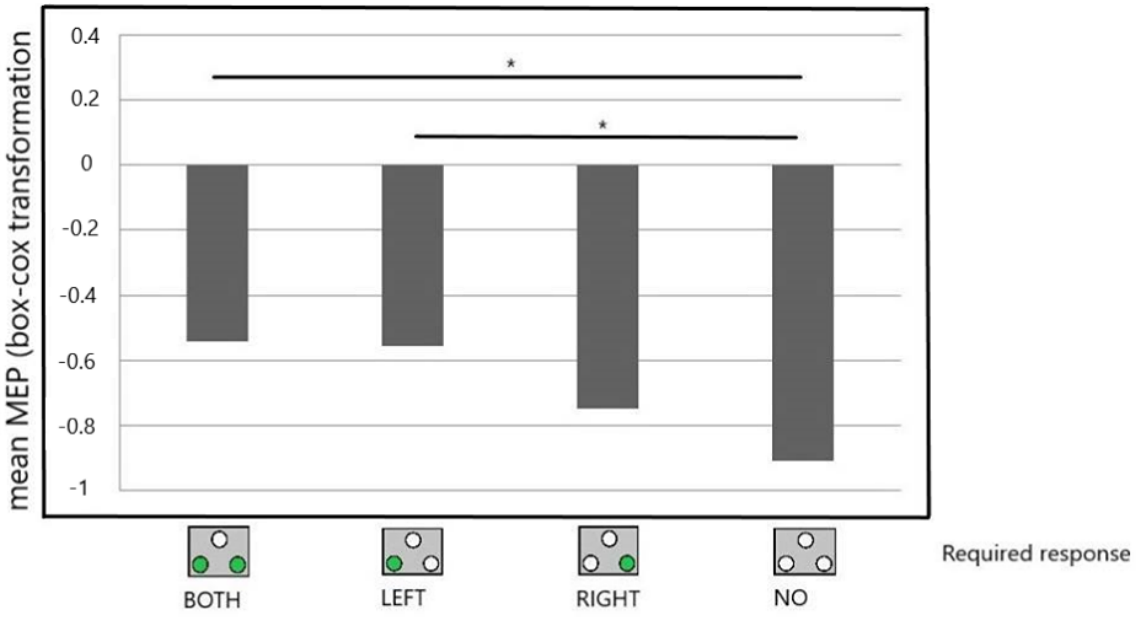

Figure 8: action selection period right hemisphere *p<0.05

Discussion

The aim of our study was to investigate if there is a difference in modulation of SICI during the preparation and action selection period of a choice reaction task between young adults and elderly. We hypothesized that there would be an age-related difference, with less modulation potential of SICI in elderly as compared to young adults. This research revealed a difference in modulation of SICI during the preparation period between younger adults and elderly but not during the action selection period of a choice reaction task.

Previous studies of age-related differences in modulation of SICI mainly reported about SICI during the resting-state (Motawar, Hur, Stinear, & Seo, 2012), showing inconclusive findings. Heise et al. (2013) showed an association between reduced resting-state SICI and a loss of modulation capacity, this possibly reflects the decrease of function of GABAa neurotransmission and can result in the loss of motor function in elderly. In contrast to this, Opie, Ridding, and Semmler (2015) showed no difference of SICI in resting muscle between younger adults and elderly, suggesting that GABAa neurotransmission is maintained with age. The inconsistencies of the results are unclear but can relate to variations in characteristics of the subject and method of the study (McGinley, Hoffman, Russ, Thomas, & Clark, 2010).
Studies about event-related SICI and age-related differences are very limited. We focused on the preparation period and action selection period of a CRT task. During healthy aging, information processing related to anticipation and preparation of a motor response changes (Sterr & Dean, 2008). Especially in CRT tasks, readiness of the motor system is affected by aging (Proctor, Vu, & Pick, 2006). This can be attributed to a slower transition from a preparatory to an executive mode of operation (Burke & Kamen, 1995). Younger adults have a higher recruitment of the frontal brain network and lateralized activation over motor regions, whereas these trends were not seen in elderly during a CRT task (Sterr & Dean, 2008). TMS studies in young adults showed a suppression of corticospinal excitability (suppression of MEP amplitude) towards the end of the preparation period in CRT tasks (Davranche et al., 2007).

During the preparation period of the CRT task, we found a significant difference between both groups for the left hemisphere only, with more inhibition for the young subjects. This could

be explained by an early suppression of corticospinal excitability in the dominant hemisphere as compared to the non-dominant hemisphere (Cuypers et al., 2013). We consider the significance of only one hemisphere could be influenced by dominance of the right hand, which was a requirement for inclusion. Further research with left handed participants is needed to confirm this statement. Davranche et al. (2007) showed that premature responses could be prevented by suppression of corticospinal excitability. We suggest that younger adults can prevent more premature responses with their right hand independent of the response. The age-related difference was also found in the study of Cuypers et al. (2013), where they found a stronger suppression of MEPs during the preparatory period for the dominant (right) FDI in young adults in comparison with elderly. In the preparatory period, less suppression of MEPs were associated with slower reaction times in elderly and is related to a decline in preparatory processes in the dominant hemisphere (Cuypers et al., 2013).

During the action selection period, no significant age-difference was found. Furthermore, no difference was found for the required responses between both hemispheres. We showed a significant difference for the left hemisphere between no response and right response with more inhibition during no response. In the right hemisphere, a significant difference was found between no response and left response and between no response and both with more inhibition during no response compared with both or left response. So, no difference of age was found during the action selection period. This result is in line with the study of Cuypers et al. (2013) where similar levels of MEP facilitation were found towards movement onset of a CRT task for both age groups. Fujiyama et al. (2012) investigated the time course of corticospinal excitability and inhibitory processes during a reaction task and found greater excitability changes just before the volitional EMG burst in young adults in comparison with elderly. The release of inhibition was of similar magnitude for both age groups, just before movement onset (Fujiyama et al., 2012). It suggests that corticospinal excitability and SICI are mediated independently during the time course of a reaction task and are affected differently by aging (Fujiyama et al., 2012). This could be related to the slowing of motor responses (Fujiyama et al., 2012).

While TMS is now a common used measurement tool for inhibition, an important limitation should be considered. It can only be used for inhibitory pathways that project to M1, because

MEPs can only be measured in this area (Levin et al., 2014). More specific, the use of TMS alone does not give a complete picture of inhibition modulation, it only measures on the GABA receptor level but does not take the concentration of GABA into account (Tremblay et al., 2013). Gao et al. (2013) demonstrated a negative correlation between age and GABA concentration with the use of MRS. It is possible that the reduction in GABA concentration with increasing age is a consequence of a decrease in the efficacy of the production in GABA (Gao et al., 2013).

In conclusion, there is a difference in modulation of SICI during the preparation period between younger adults and elderly for the left hemisphere. This suggests that only the dominant hemisphere is affected by aging, and more specific GABAa-ergic modulation. During the action selection period, no difference of groups was found. We encountered a lack of studies with elderly as the study population. Therefore, we recommend future studies to examine the influence of aging on the motor system.

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VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
06/10/2017	Overlopen inhoud masterproef deel 2	Promotor: Copromotor: Student(e): Vanuytven Student(e): Raadgiep
08/11/2017	Uitleg en uitvoeren data verwerking	Promotor: Copromotor: Student(e): Vanuytven Student(e): Raadgiep
15/11/2017	Uitleg en uitvoeren data analyse	Promotor: Copromotor: Student(e): Vanuytven Student(e): Raadgiep
17/03/2018	Uitleg en bespreken resultaten	Promotor: Copromotor: Student(e): Vanuytven Student(e): Raadgiep
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