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Faculteit Geneeskunde en Levenswetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The influence of age on the gamma-aminobutyric acid concentration of homologue sensorimotor cortices: a 1H-MRS study

Nicolas Van Beeumen

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij musculoskeletale aandoeningen

PROMOTOR :

Prof. dr. Raf MEESEN

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Prof. dr. Raf Meesen, the promotor, who oversees this manuscript. The feedback provided by him during the internship assisted me in understanding the scientific process.

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Dra. Stefanie Verstraelen, the supervisor during the internship. Assisting her, gave me insight in the performance and interpretation of TMS and EMG measurements.

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Research context

In 2016, 18.3% of the Belgian population was 65 and older, furthermore the current life expectancy is about 81 years old for those born that year (Belgian Federal Government, 2016, 2017b). In this aging population, there was a nine percent increase in the people working at 50 and older between the years 2000 and 2015 (Belgian Federal Government, 2017a). Furthermore, the age-associated expenditure of the Belgian government to healthcare and long-term care is expected to increase (this also implies to the rest of the European Union) (Rechel et al., 2013). Aging exerts a large socioeconomic impact on society, therefore, research towards this topic is crucial.

Comparing older to younger adults, structural changes (e.g. decrease in brain volume) and functional changes (e.g. slowing of performed movements) become evident (Glisky, 2007; Seidler et al., 2010).

Age exerts an influence on the neurotransmitter concentration as depicted by (Gao et al., 2013). However, it is not well known if both hemispheres are affected at the same extend. This manuscript focusses on the influence age exerts on the inhibitory neurotransmitter GABA of both the sensorimotor cortices. The following research question is attempted to be answered: is there an asynchronous deterioration of the GABA concentration with advancing age?
Possible future implications: is there a link between these results and the functional changes mentioned earlier?

This manuscript is part of an ongoing research project called 'sensorimotor control and aging' of the research unit "Movement Control & Neuroplasticity" Laboratory for Motor Control of the Faculty of Kinesiology and Rehabilitation Sciences. The head of this research group is prof. Stephan Swinnen. This study was commissioned by the University of Leuven (KU Leuven) in close collaboration with the University of Hasselt (UHasselt). The author declares to have no conflict of interest with this project.

At the beginning of the second part of the master thesis, the data acquisition was already initiated. Therefore, I didn't contribution to the actual research design, methods and recruitment. The unsuitable timing of the data-acquisition resulted in me not assisting during this part of the study. As compensation I did an internship by dra. Verstraelen, where I assisted her with EMG, TMS and

MRI measurements. Similarly, this study researched the underlying mechanisms of aging. The internship encompassed more than 38 hours of experimental work and involved 20 subjects.

At the start of this academic year, dr. Cuypers discussed with me the data he had at his disposal. With that in mind, I wrote down my own research question and a rendition of how I thought the data were acquired. If there were inconsistencies with the real data-acquisition, corrections were applied by dr. Cuypers. The manuscript below is fully written by me, including the R-code used for the statistical processing. If necessary, feedback for the R-code script was given by dr. Cuypers. The data, "Figure 1" and "Figure 2" used in this manuscript are made by dr. Cuypers.

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The influence of age on the gamma-aminobutyric acid concentration of homologue sensorimotor cortices: a ^{1}H-MRS study.

Abstract

Background: Aspects of motor performance change with advancing age. Studies using transcranial magnetic stimulation (TMS) observed an altered interhemispheric inhibition in elderly in the primary motor cortex. TMS does not provide information on the neurotransmitter concentration, the primary inhibitory neurotransmitter being gamma-aminobutyric acid (GABA). Magnetic resonance spectroscopy (MRS) research mainly revealed a negative correlation between GABA concentration and age. However, research mainly focused on frontal and parietal regions with very limited focus on the primary motor cortex.

Objectives: The first objective was to investigate the effect of aging by comparing the GABA concentrations of young and older adults within the same hemisphere. The second objective was to investigate lateralization by comparing the GABA concentrations of different hemispheres within the same age group.

Participants: 50 healthy right-handed volunteers, with 25 subjects in the young group (18-33 years old) and with 25 subjects in the older group (60-74 years old).

Measurements: Proton magnetic resonance spectroscopy (^{1}H-MRS) at 3.02 ppm is used to measure the GABA concentration of the sensorimotor cortices. More specific, voxels were centered over the two hand knob areas of the left and the right hemispheres. ^{1}H-MRS is executed using a MEGA-PRESS sequence. The outcome measures are tissue corrected for the amount of gray matter, white matter, cerebrospinal fluid and macromolecule contribution.

Results: The mixed model revealed only a significant main effect of age ($p = 0.025$). Hemisphere ($p = 0.596$) and the age*hemisphere interaction ($p = 0.923$) were not significant.

Conclusion: The GABA concentrations decline with advancing age in the sensorimotor cortices, but no significant difference in the GABA concentrations is observed between the homologue regions of the same age group.

Keywords: GABA, aging, magnetic resonance spectroscopy, sensorimotor cortex

Introduction

Motor performance declines with advancing age (Voelcker-Rehage, Reuter, Vieluf, & Godde, 2013). Moreover, older adults show less asymmetry in handedness, meaning that they perform specific tasks equally accurate and paced with both hands. In contrast, young adults perform

better with their preferred hand (Raw, Wilkie, Culmer, & Mon-Williams, 2012). Furthermore, it was shown that manual dexterity is declined in older adults (B. W. Fling & Seidler, 2012), that older adults perform bimanual asynchronous tasks poorer than young adults, and that these tasks deficits can be at least partly explained by elevated interhemispheric inhibition (Bangert, Reuter-Lorenz, Walsh, Schachter, & Seidler, 2010; Brett W. Fling et al., 2011).

The above mentioned interhemispheric inhibition, is partially mediated by gamma-aminobutyric acid type B ($GABA_B$-ergic) neurons (Daskalakis, Christensen, Fitzgerald, Roshan, & Chen, 2002; Irlbacher, Brocke, Mechow, & Brandt, 2007). GABA, the primary inhibitory neurotransmitter of the central nervous system, binds to these $GABA_B$ receptors, which in turn activates a G protein. The G protein does the following: it inhibits adenylyl cyclase, causes an inhibition of the calcium channels at the pre-synaptical level, and leads to an activation of the inward rectifying potassium channels at the post-synaptical level (Chu, Albin, Young, & Penney, 1990; Gassmann & Bettler, 2012; Kumar, Sharma, Kumar, & Deshmukh, 2013; Yamada, Saitow, Satake, Kiyohara, & Konishi, 1999).

Until now, research focusing on age-related changes in inhibitory processing during motor performance, was mainly conducted with Transcranial Magnetic Stimulation (TMS), investigating the modulation of the GABA receptors targeting the primary motor cortex. For example, it was revealed that after the starting signal of a rapid left index finger abduction task, the measured inhibitory interactions between the left dorsal premotor cortex and the right primary motor cortex (PMd_L-$M1_R$) became facilitatory compared to the rest condition, in the older group, but not in the young group (Hinder, Fujiyama, & Summers, 2012). In another study, an age-related decrease in interhemispheric inhibition was observed between the primary motor cortices ($M1_L$-$M1_R$) during a low-strength isometric contraction task (Talelli, Waddingham, Ewas, Rothwell, & Ward, 2008). These alterations in interhemispheric inhibition between PMd_L-$M1_R$ and between $M1_L$-$M1_R$ couldn't be detected in a resting condition (a controlled condition; not asleep). As mentioned before, these changes in GABA-ergic function were mainly assessed with TMS and refer to changes on the GABA receptor level. However, research investigating changes in the GABA neurotransmitter concentration (further referred to as GABA levels) in the brain are limited. Therefore, this work will explore age-related changes in GABA levels in homologue motor areas within the human brain.

GABA levels can be measured in vivo by means of magnetic resonance spectroscopy (MRS). This technique allows for the direct and non-invasive detection of endogenous GABA in a chosen volume of the brain (N. A. Puts & R. A. Edden, 2012). The radiofrequency signals that MRS detects are, however, not specific to the location. More specifically, MRS cannot differentiate between the GABA available in the synaptic cleft or within the neuron (Porges, Woods, Lamb, et al., 2017). Furthermore, the measurement signal is highly sensitive to the parameters chosen for the acquisition, such as for example the volume of the voxel, the field strength and the pulse sequence, for a full overview of the influencing factors consult (Alger, 2010).

Although currently the number of MRS studies focusing on age-related changes in GABA levels is rather limited, evidence suggests that GABA levels decrease with advancing age. The studies of (Gao et al., 2013; Porges, Woods, Edden, et al., 2017), both showed a negative correlation between age and the GABA levels, for the same regions within the frontal and parietal lobe. In contrast, the study of Ghisleni showed no correlation between age and the GABA levels in the frontal lobe (Ghisleni et al., 2015). However, it has to be noted that voxel placement was slightly different as compared to previously described studies. Another recent study with conflicting results is the study of Mooney, suggesting there is no correlation between age and the GABA levels in the primary motor cortex (Mooney, Cirillo, & Byblow, 2017). However, the small voxel size used in this study could have detrimental effects on the signal-to-noise ratio (SNR) (Mullins et al., 2014), making it very difficult to draw proper conclusions from this work. Taking into account the gender effect, research showed that some brain regions in women are subjected to a greater age-related decline in GABA levels (Gao et al., 2013). The goal of this study is to compare age-related GABA levels in homologue areas of the brain, while recent research was limited to the investigation of age-related changes in GABA levels in one hemisphere.

Here, the sensorimotor cortex (SM) is studied, by centering the voxel over the hand knob of the primary motor cortex (M1). M1 is the key region for voluntary motor activation and is involved in several processes. For example, the M1 is involved in implicit motor sequence learning (Pascual - Leone, Grafman, & Hallett, 1994). There is anatomical segregation of the proximal and distal movements in this part of the cortex (Luppino, Matelli, Camarda, Gallese, & Rizzolatti, 1991). The M1 plays an important role in segmenting actions, planned by other motor areas, into more simplified movements (Porter & Lemon, 1995). All this evidence points out that M1 is an important region to investigate.

In reality, some compromises will be made when studying M1 with MRS, due to the inherently low SNR of GABA. To counteract this fact a larger voxel is commonly used (30 x 30 x 30 mm^3) to reliably measure the GABA levels (Mullins et al., 2014). When M1 is measured with this voxel size (which is larger than M1), the measurement will include some part of the somatosensory cortex (Porro et al., 1996). Hence, there will be further referred to the sensorimotor cortex as this is a more accurate description.

To further unravel the role of SM and its functional evolution due to aging, the following research questions are formulated: (1) Does GABA levels differ between healthy young and older volunteers in the SM? And (2) are there differences in GABA levels between homologue regions of healthy volunteers? Based on the literature described above the following hypotheses are formulated: (a) GABA levels are expected to decrease with advancing age, (b) in young adults (but not in older adults) a hemispheric asymmetry in GABA levels is expected. More specific, it is expected that GABA levels are higher in the dominant hemisphere in young adults. In older adults, it is expected that hemispheric asymmetry is reduced or absent as result of a suggested reduced motor lateralization (Przybyla, Haaland, Bagesteiro, & Sainburg, 2011).

Material and Methods

Subjects

A total of 50 healthy right-handed volunteers are enrolled in this study. The young group consists of 12 females and 13 males. The age-range of the young group is between 18 and 33 years old, with a mean age of 22 years old. The older group consists of 13 females and 12 males. The age-range of the older group is between 60 and 74 years old, with a mean age of 67 years old. Inclusion criteria are: subjects must be between the ages 18 and 35 or between 60 and 75 years old, right handed and healthy. Handedness is assessed by the lateralization quotient of the Edinburgh Handedness Inventory (Short Form) (J. Veale, 2017; J. F. Veale, 2014). A full overview of the subject specifications is presented in Table 1.

Table 1

Subject specifications

	Young group	Old group
Number of subjects	25	25
Men	13	12
Mean age (± SD) [years]	22.08 (± 4.04)	67,48 (± 4.37)
Age-range [years]	18 – 33	60 – 74
Lateralization Quotient (± SD)	87.64 (± 13.92)	94.43 (± 10.15)

SD = Standard deviation

Exclusion criteria are: a known history of- or current neurological disease or mental disorder, playing an instrument (Khose et al., 2012) or taking any GABA-influencing drug as described by (Amunts et al., 1997). Subjects are excluded for any (potential) MRI contra-indications. The subjects are not allowed to smoke or drink alcohol or take in caffeine the day before the measurement, because the acute intake of these substances can influence the GABA levels (Donahue et al., 2014; Gomez et al., 2012; Radcliffe, Fisher, Gray, & Dani, 1999; Xu, Liu, Pekar, & Lu, 2015). All subjects signed an informed consent prior to participation in the study.

MRI and MRS data acquisition specifications

The GABA levels are measured with a proton magnetic resonance spectroscopy (^{1}H-MRS), this is currently the only technique that allows direct, non-invasive detection of endogenous GABA in vivo in the brain (Nicolaas AJ Puts & Richard AE Edden, 2012). ^{1}H-MRS is carried out on a Phillips 3T Achieva Magnetic Resonance scanner, with a 32 channel receiver head coil. For the localization of the region of interest (ROI), a 3D T1-weighted anatomical image was used.

The ROI's of this study are the right and left sensorimotor cortex voxels (SM_R and SM_L respectively) and have the following dimensions 30 × 30 × 30 mm³. These voxels are centered over the right and left hand knobs, parallel to the longitudinal fissure. The superior surface of these voxels are parallel to the cortical surface, in the coronal and axial views (Greenhouse, Noah, Maddock, & Ivry, 2016). Figure 1 represents a standard placement of the voxel in SM_L.

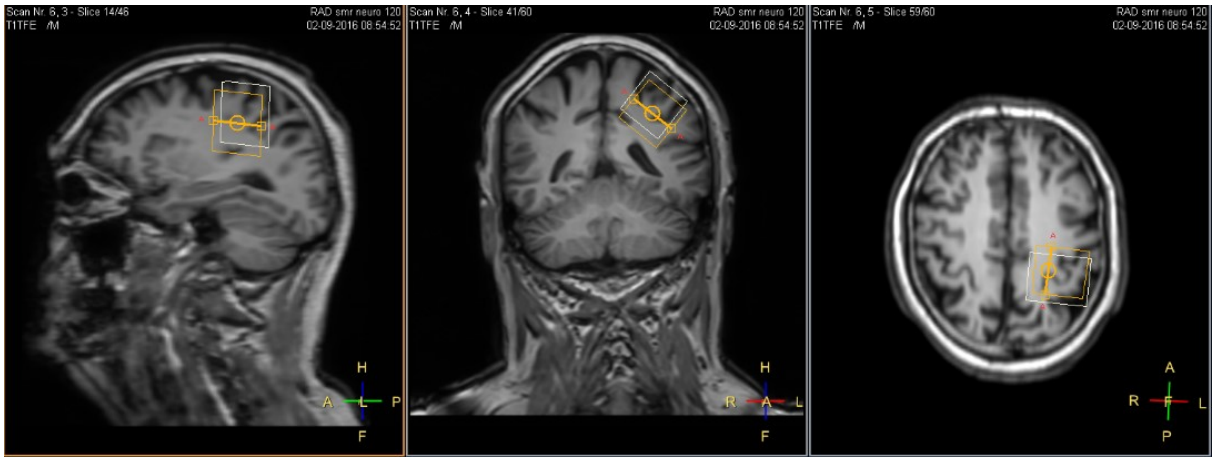

Figure 1. Standard placement of a 30 × 30 × 30 mm^3 voxel of the left sensorimotor cortex. The three images display the same voxel, only displayed from another viewpoint: (A) sagittal plane, (B) frontal plane, (C) transversal plane.

A MEGA-PRESS sequence with the following parameters is used: TR = 2000 ms; TE = 68 ms; 320 averages. The acquisition time for a single voxel is 11 minutes 12 seconds. The GABA-edited MRS data are processed following the Gannet 3.0 GABA analysis toolkit guidelines integrated in MATLAB (Gannet, 2017; MathWorks, 2017). A data quality check is performed: the GannetLoad and GannetFit data analyzing steps. In case of a field drift or subject movement, this will appear in the data as a non-zero slope or discontinuation of the residual water signal frequency respectively. The Gannet toolkit software automatically rejects data points, where the parameter fit (area, full width at half maximum, phase or frequency) deviates more than three standard deviations of the mean fit (Gannet, 2017). Figure 2 (in Appendix) displays the MRS spectrum of one of the subjects, representing an average data sample that would be subjected to the quality check.

The outcome acquired by the spectroscopy is the ratio of the GABA levels against an internal reference, water (H_2O). This outcome is tissue corrected, meaning there is a correction for the amount cerebral spinal fluid (CSF), gray matter (GM) and white matter (WM) present in the voxel (Harris, Puts, & Edden, 2015). However, this tissue correction uses some factors that need further clarification: α, the mean GM fraction (μ_{GM}) in a voxel and the mean WM fraction (μ_{WM}) in a voxel. α is set at 0.5 and represents the ratio of GABA levels in WM to GM. μ_{GM} and μ_{WM} are calculated for each group individually, because the amount of CSF increases and the amount of GM and WM decreases with advancing age (Giorgio et al., 2010; Porges, Woods, Lamb, et al., 2017). When the spectrum is acquired some macromolecules are coedited, the correction formula has a factor

taking into account the macromolecule contribution (Mullins et al., 2014). No separate measurement for these macromolecules is made, therefore the GABA levels are artificially corrected. Creatine nor *N*-acetyl aspartate are used as internal reference measures for this study, due to the influence age exerts on both the metabolites (Haga, Khor, Farrall, & Wardlaw, 2009).

Study design

Figure 3 represents the stages passed in chronological order by the subjects.

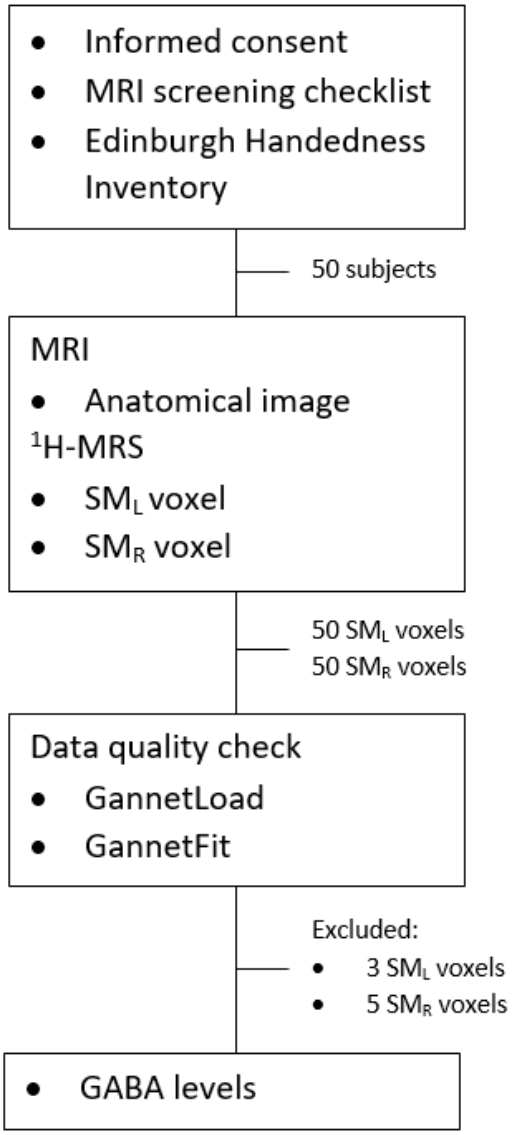

Figure 3. Overview study design. MRI = magnetic resonance imaging, ^{1}H-MRS = proton magnetic resonance imaging, SM_L = left sensorimotor cortex, SM_R = right sensorimotor cortex.

Statistics

All statistical analyses are performed with R (R Core Team, 2017). Outcomes are given as means with standard deviations (±SD). A mixed model is used to describe the influence of age and hemisphere on the GABA levels. The fixed effects used in the models are age, hemisphere and the interaction between age and hemisphere. The subjects themselves will be taken in consideration as random effects in the mixed models. Age (young; old) and hemisphere (SM_L; SM_R) are both presented as dichotomous variables. The GABA levels are a continuous outcome variable ($GABA/H_2O$). The residuals are checked for a normal distribution with a normal Q-Q plot and homoscedasticity is checked by plotting the residuals against the fitted response of the model.

Medical ethics

This study was approved by the Commission for Medical Ethics, UZ Leuven
(Project number: S58333).

Results

The lateralization quotient reveals no significant difference between the handedness of both groups ($p > 0.05$). After quality check, data of one young subject (one SM_L voxel) and data of five older subjects (five SM_R voxels and two SM_L voxels) were excluded. Consult Appendix Table 2 and Table 3 for a full overview of the GABA levels and lateralization quotients of the young and old group respectively.

The mixed model reveals only a significant main effect of age ($F = 5.36$, $p = 0.025$). The GABA levels in the young group measure 2.0872 (SD = ±0.0554) and the old group measure at average 0.2565 lower than in the young group (1.8307 ±0.0554). Hemisphere ($F = 0.29$, $p = 0.596$) and the age*hemisphere interaction ($F = 0.01$, $p = 0.923$) are not significant. Figure 4 displays the GABA levels sorted by the different groups.

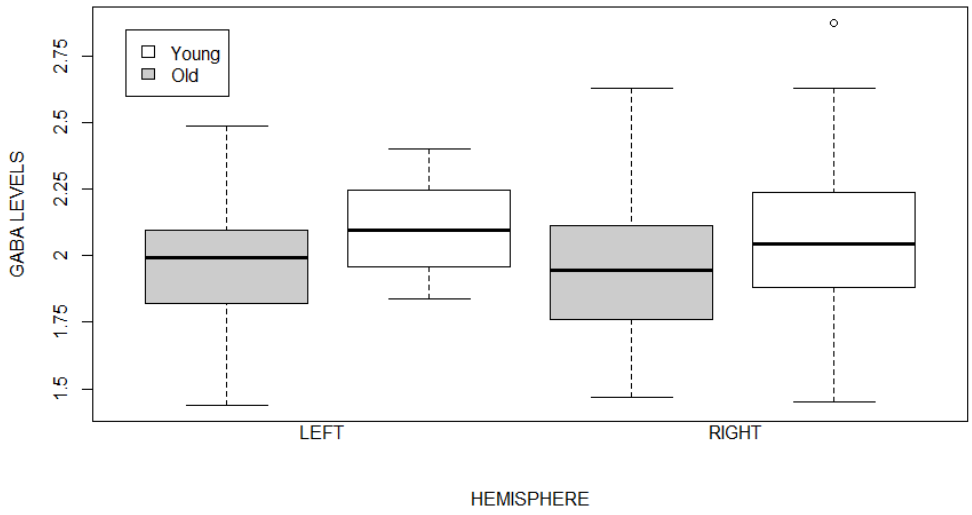

Figure 4. GABA levels by hemisphere & age group.

Discussion

In the present study, no significant difference in GABA levels between hemispheres is found. This is currently the only study comparing the GABA levels of both hemispheres in the human brain, these results can not be cross validated.

Furthermore, there is no interaction effect of hemisphere and age, implying that the GABA levels will not further be influenced by specifing the hemisphere. This as opposed to the study of Minkova, who did find an asymmetry in the amount of gray matter loss of the post central gyrus within the sensorimotor cortex (Minkova et al., 2017). They reported a greater age related decline left compare to right.

When comparing the results with the available research, a similar decline in GABA levels is observed with advanced age (Gao et al., 2013; Porges, Woods, Edden, et al., 2017). There the two previous mentioned studies used the same voxel placement (with the voxel placed on the median aspect of the axial plane). In this study, the voxel is placed more lateral on the handknob area.

The GABA levels are liable to change and some undelying mechanisms already have been explored. In animal studies the GABA levels in aging mice declined in the auditory cortex, the decline was attributed to a decrease in the mRNA of glutamic acid decarboxylase (GAD) 65 and GAD 67 but also to a decrease in GAD 67 protein. GAD 65 and GAD 67 are enzymes that

decarboxylate glutamate to form GABA (Burianova, Ouda, Profant, & Syka, 2009; Ling, Hughes, & Caspary, 2005).

The MRS measurement performed here, is on subjects in rest and no significant difference is apparent between the GABA levels of both hemipheres. This set up does not exclude the possibility that one might observe a difference in the change in GABA levels while performing a task, because the GABA levels decrease in the contralateral hemisphere when a subject performs a motor learning sequence of 30 minutes with one hand (Floyer-Lea, Wylezinska, Kincses, & Matthews, 2006). Additionally, changes in the inhibition between young and older adults in TMS studies are only apparent during or after the execution of a task, but not at rest (Hinder et al., 2012; Talelli et al., 2008).

The design for this study is a cross sectional design, comparing two different age groups with each other. A more suited design would be a prospective design, following the same set of subject over a prolonged time. This would not be subjected to interindividual differences. This design has some practical obsticals such a loss of follow up, because this experiment would go over several decenia. Secondly, this technology is still developing with advances in aswell hardware as software, what would mean comparing different experimental set ups.

Another limitation of this study is the tissue correction formula of (Harris et al., 2015). Specifically the macromolecule contribution of this formula is rather simple, stating the macromolecule contribution as a single factor. This presumes that the macromolecule contribution is a constant and not subjected to possible influences of aging.

The current literature on the influence of age on the GABA levels suffers from mixed results. A difference in sample size may contribute to this, ranging between 35 and 100 subjects studied, by influencing the power of aforesaid study (Gao et al., 2013; Grachev Igor & Apkarian, 2008). Therefore, a post-hoc analysis calculating the power is made, according to the example of (Brysbaert & Stevens, 2018). The current mixed model used in this study (including GABA levels and age, but not hemisphere or interaction of age and hemisphere) has an estimated power of 64.40%. This means that despite the significant difference in GABA levels between the age groups, future research should include a larger sample size to minimize the chance on a type II error.

The results give more insight on the influence of age on the inhibitory system. Currently, little is known on the resting state GABA levels of the sensorimotor cortex and with which factors it correlates. This could be the result of a possible publication bias. Further research is nessecary to evaluate the impact of the decrease in GABA levels on the healthy population.

Conclusion, the GABA levels decline with advancing age in the sensorimotor cortices, but no significant difference in the GABA levels is observed between the homologue regions of the same age group.

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Appendix

Table 2

Overview data young group

Subjects	Left M1	Right M1	Oldfield
P01	N/A	2.045086377	86.67
P02	1.933156574	1.882742081	100.00
P03	1.958967476	2.222116866	100.00
P04	1.985068313	2.877953617	84.62
P05	2.144670053	2.068044855	60.00
P06	2.350240954	2.444569600	100.00
P07	2.314333175	1.808572646	100.00
P08	1.891700660	1.876893881	80.00
P09	2.161963667	1.880310702	100.00
P10	2.239575696	1.807571132	100.00
P11	2.401022538	2.027224630	88.89
P12	1.960832135	2.628852082	100.00
P13	1.999162220	1.599350878	70.00
P14	2.252656429	2.123254285	84.62
P15	1.837657641	1.974942488	100.00
P16	2.158478893	1.832793336	100.00
P17	1.933598769	1.449854121	86.67
P18	2.268043821	2.059502163	100.00
P19	2.169573705	2.238976587	80.00
P20	2.215328454	1.922562181	100.00
P21	1.958524963	2.016708395	60.00
P22	1.989417199	2.311181309	80.00
P23	1.921873269	2.469587210	57.14
P24	2.275451914	2.261328640	86.67
P25	2.045438452	2.082444410	85.71

N/A: not available, this subject data has been excluded

Table 3

Overview data old group

Subjects	Left M1	Right M1	Oldfield
P01	1.954006854	1.984648402	100.00
P02	N/A	N/A	67.00
P03	1.706285262	1.634203277	100.00
P04	1.765996977	2.211586101	100.00
P05	1.580506814	N/A	100.00
P06	N/A	N/A	100.00
P07	1.755897622	1.598986538	100.00
P08	2.070725504	1.865964007	90.00
P09	1.862367639	2.009602764	81.82
P10	2.305558394	2.112392209	100.00
P11	2.212907368	N/A	100.00
P12	2.084429879	1.516458446	80.00
P13	2.168430901	N/A	100.00
P14	2.087084173	1.987987408	100.00
P15	2.10498053	1.833576681	70.00
P16	1.863642731	1.749457607	100.00
P17	2.486512965	2.631727508	100.00
P18	1.778477366	1.817355349	100.00
P19	2.079757508	1.771951756	100.00
P20	1.912843985	2.111077233	81.82
P21	1.992790616	2.095319331	90.00
P22	1.938557809	2.271635442	100.00
P23	2.020884225	2.255427905	100.00
P24	1.436778918	1.907235061	100.00
P25	2.22204057	1.468468286	100.00

N/A: not available, this data point has been excluded

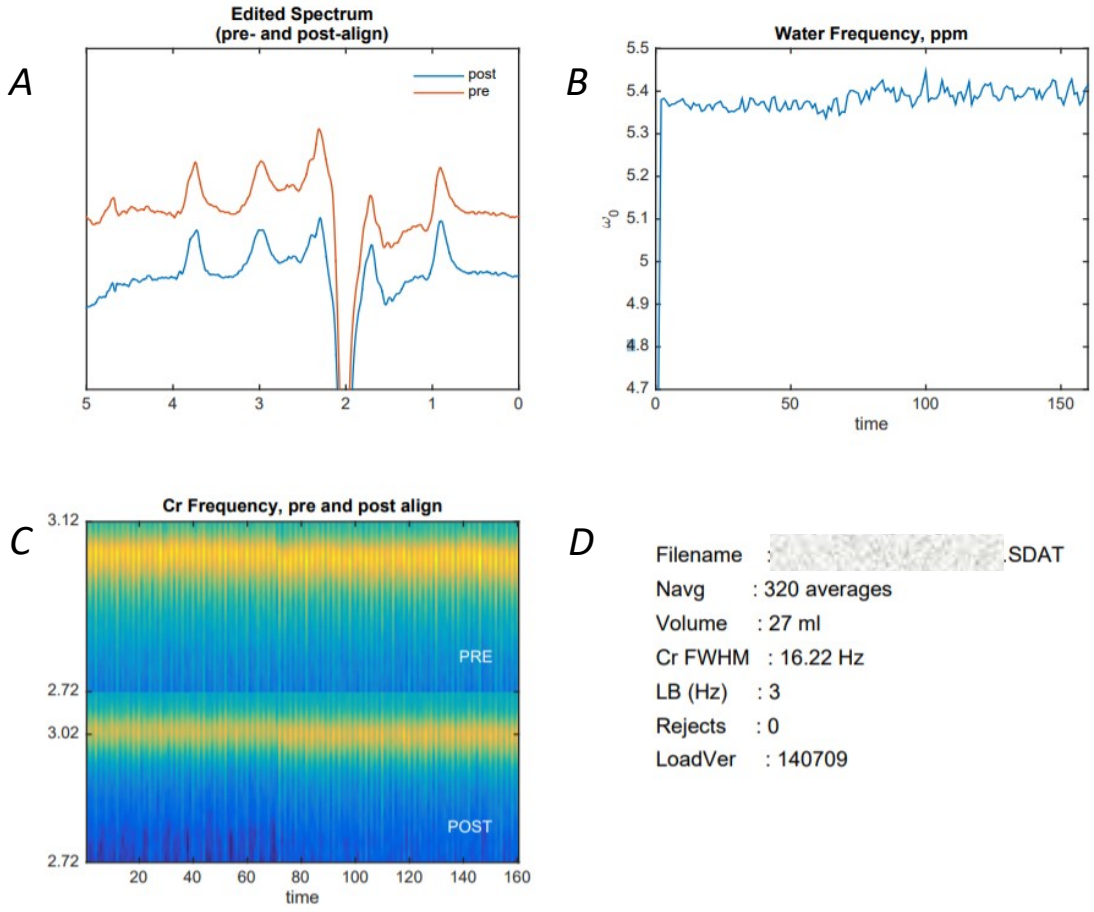

Figure 2. The MRS spectrum of a subject. This is a GannetLoad output which passed the quality check. A. GABA-edited difference spectrum, B. residual water frequency, C. Creatine signal over time, D. descriptive variables.

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KNOWLEDGE IN ACTION

VOORTGANGSFORMULIER WETENSCHAPPELIJKE STAGE DEEL 2

DATUM	INHOUD OVERLEG	HANDTEKENINGEN
30/8/2017	Aanwezig: dr. Koen Cuypers, Nicolas Van Beeumen Inhoud: verwachtingen MP 2, beschikbare data, keuze statistisch programma	Promotor: Copromotor: Student(e): Student(e):
3/12/2017 en 4/12/2017	e-mail: Feedback inleiding + vragen omtrent de methode	Promotor: Copromotor: Student(e): Student(e):
5/12/2017	e-mail: Gecorrigeerde inleiding + Feedback methode	Promotor: Copromotor: Student(e): Student(e):
12/12/2017 t.e.m. 20/12/2017	e-mail: Feedback statistische verwerking in R	Promotor: Copromotor: Student(e): Student(e):
16/1/2018	Onder leiding van dr. Koen Cuypers een 1H-MRS meting bijwonen	Promotor: Copromotor: Student(e): Student(e):
18/1/2018 t.e.m. 30/1/2018	e-mail: Feedback resultaten + vragen omtrent geëxcludeerde data	Promotor: Copromotor: Student(e): Student(e):
24/4/2018	e-mail: Update discussie en conclusie	Promotor: Copromotor: Student(e): Student(e):
16/5/2018 t.e.m. 19/5/2018	e-mail: Feedback volledige thesis	Promotor: Copromotor: Student(e): Student(e):
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Jaar: **2018**

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