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ORIGINAL RESEARCH

Reduced spontaneous low frequency oscillations as measured with functional near-infrared spectroscopy in mild cognitive impairment

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Abstract
Spontaneous low frequency oscillations (LFO) in functional imaging data have gained increased interest in the study of cognitive decline. Persons diagnosed with mild cognitive impairment (MCI) and Alzheimer's disease (AD) display alterations in their amount of LFO in various brain regions. This is commonly interpreted as disruptions in the autoregulation of the cerebral microvascular system. In the present study LFO (0,07–0,11 Hz) were measured with 52-channel near-infrared spectroscopy (NIRS) in 61 healthy elderly persons (70–76 years), 54 MCI subjects (70–76 years) and 25 healthy young controls (21–48 years) during rest over the frontal and the parietal cortex. Both MCI and healthy elderly controls showed less LFO in the frontal cortex as compared to young subjects. For the parietal cortex a decrease in LFO could be observed for the MCI group in comparison to healthy elderly subjects. Correlations of more LFO with worse performance in neuropsychological tests point to compensatory processes. LFO measured with NIRS might be especially suited for longitudinal studies aiming at predicting cognitive decline.

Keywords Near-Infrared Spectroscopy · Mild cognitive impairment · Low frequency oscillations

Introduction

Worldwide, Alzheimer's disease (AD) is the most common form of neurodegenerative disorders (Desai and Grossberg 2005). While there is no cure to date, one important aim is to detect cerebral changes as early as possible. Current and possible future treatments will be more effective if irreversible neural damage is as small as possible (Winblad et al. 2016). When talking about early detection of cognitive decline the concept of mild cognitive impairment (MCI) is of utmost importance. First proposed in 1999 (Petersen et al. 1999) it refers to a condition in which the patient displays cognitive impairment but does not yet fulfill the criteria for dementia. The subtype of amnestic MCI (aMCI) specifically refers to persons showing mainly a reduced memory performance. Amnestic MCI is widely regarded as a prodromal stage of AD (DeCarli 2003). While a high percentage of persons categorized as aMCI progress to AD in the next 10 years, a considerable number never develops dementia (Jicha et al. 2006; Petersen 2004). To define predictors for this development is therefore an important topic. In this field of early detection, functional imaging is an especially promising approach as functional changes might occur even before neural atrophy. Among functional imaging methods near-infrared spectroscopy (NIRS) might be especially suited for psychiatric settings (Fallgatter et al. 2004).

Slow oscillation data derived from functional imaging methods have gained increasing interest in the last years. They can be observed with most techniques measuring cerebral hemodynamics and metabolism with sufficient temporal resolution, such as functional magnetic resonance imaging (fMRI, e.g. Biswal et al. (1995)), transcranial doppler

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sonography (TCD, e.g. Zhang, Zuckerman, Giller, and Levine (1998)) and NIRS (e.g. Obrig et al. (2000)). Throughout all different methods these oscillations share four characteristics: (a) they occur spontaneously, with and without stimulation (Obrig et al. 2000), (b) they are distinctively slower than oscillations caused by heartbeat (1 Hz) or respiration (0,2 – 0,3 Hz; Elwell et al. (1996)), (c) they can be altered by pathological conditions, pharmacological interventions and cognitive and physical stimulation (Schroeter et al. 2005; van Beek et al. 2012; Vermeij et al. 2014), and (d) they occur at the same frequency as LFO in blood pressure (van Beek et al. 2012; Vermeij et al. 2014; Zhang et al. 1998).

Obrig et al. (2000) established the measurement of slow oscillations over the human visual cortex with NIRS. Peaks in the oscillation spectra of oxygenated (O_2Hb) and deoxygenated hemoglobin (HHb) were observed at 0,03 Hz (very low frequency oscillations, VLFO) and around 0,1 Hz (low frequency oscillations, LFO, also known as Mayer Waves (Julien 2006)), both during rest and a visual checker board stimulation. They concluded that NIRS could be used for a local noninvasive assessment of microvascular autoregulatory mechanisms in the adult brain.

Despite numerous studies concerning VLFO and LFO, their physiological origins are still not fully understood. When examining oscillations simultaneously in peripheral blood pressure and central oxygenation with NIRS, a coherence between the two measurements becomes evident (van Beek et al. 2012; Vermeij et al. 2014). In a combined NIRS/fMRI study Tong and Frederik (2010) could differentiate the contribution of central vasomotion, systemic hemodynamics (blood pressure) and neuronal activation on LFO. According to their results, LFO seem to be rather caused by hemodynamics than by neuronal activity and are a more global than regional phenomenon. LFO measured with NIRS reflect therefore mostly the global cerebral blood flow and spontaneous fluctuations in cerebral oxygenation.

In the aging brain, cerebral vessels become stiffer. Simultaneously the metabolic rate for oxygen and cerebral glucose decreases (Farkas and Luiten 2001). In line with these findings Schroeter et al. (2004) observed less LFO during a NIRS measurement over the visual cortex in a group of elderly subjects as compared to a younger group. Elderly subjects who suffer from cerebral microangiopathy, a disease which increases small vessel stiffness, display even less LFO than healthy elderly controls (Schroeter et al. 2005).

Cerebral blood flow is also impaired in AD (Wu et al. 2005). Among other things amyloid beta 42 causes cerebrovascular dysfunction and aggregates in the small vessels (Han et al. 2008). By assessing VLFO and LFO with NIRS and TCD during a sit-stand maneuver van Beek et al. (2012) observed an altered transfer of the changes in cerebral blood flow velocity to cortical oxygenation in patients suffering from AD. Additionally they found increased LFO in the AD group over the frontal cortex in general. This can be interpreted as another indication for changes in the cerebral microvasculature in AD. As Schroeter et al. (2005) also found LFO to correlate with executive function and verbal learning, the assessment of spontaneous oscillation data with NIRS seems to be especially suited for studies tackling early detection methods for dementia.

Until now no studies examined LFO in persons fulfilling the criteria of MCI using NIRS though there are some using fMRI. Zhao et al. (Zhao et al. 2015, 2014) observed a decreased low-frequency fluctuation signal (0,01 – 0,08 Hz) in patients classified as aMCI in the left superior temporal gyrus, the right middle temporal gyrus, the right inferior parietal lobe, and the right postcentral gyrus. Altered oscillations correlated with gray matter loss. Additionally they observed increased oscillations in frontal regions interpreting this finding as neural compensation.

The present study is the first to examine LFO with NIRS using more than four channels in patients classified as MCI, age matched healthy elderly subjects and a young comparison group. It is also the first NIRS study to compare different cortical regions in this respect. The aim was on the one hand to identify differences in LFO relating to age and cognitive status and on the other hand to examine if these differences vary between the frontal and the parietal cortex, two brain regions that show alterations early in the course of cognitive decline. Former studies with fMRI suggest a pattern of increased LFO in the frontal and decreased LFO in the parietal lobe in persons classified as MCI (Zhao et al. 2015, 2014). If this pattern also emerges with NIRS it could be used as a prediction parameter for cognitive decline in future studies.

Methods

Subjects

The data of 140 subjects were analyzed for the present study. Twenty-five of them belonged to a younger group with a mean age of 34,9 ± 7,4 years (for details see Table1). The elderly group consisted of 115 persons divided into two subgroups: The elderly healthy control group (n = 61; 73,34 ± 1,7 years) and a group suffering from MCI (n = 54; 73,91 ± 1,7 years; for details see Table1).

Data for the elderly subjects are part of the VOGEL-study (Polak et al. 2017), a longitudinal study for the early detection of cognitive decline at the department of Psychiatry, Psychosomatics and Psychotherapy at the University Hospital Würzburg. Data for the younger participants are the healthy control group of the WAS-project (Würzburger Adipositas Studie), studying the effect of gastric stapling on the central nervous system and cognition at the University

Table 1 Sample characterization

		Healthy		Statistics
	MCI	Elderly	Young	
N	54	61	25	
Age	73.91 ± 1.8	73.34 ± 1.7	34.92 ± 7.4	
Sex m/f	29 / 25	24 / 37	6 / 19	$X^2 = 6.53$, $p < .04$
MMSE	28.81 ± 1.3	29.13 ± 1.0		$t_{113} = 1.46$, $p = .15$
DemTect	14.96 ± 2.5	16.87 ± 1.6		$t_{113} = 4.87$, $p < .001$
Hypertension	36	33		$X^2 = 1.89$, $p = .17$
HIS	0.65	0.67		$t_{113} = 0.24$, $p = .82$
Med BP	34	38		$X^2 = 0.01$, $p = .94$
Med D	7	2		$X^2 = 3.72$, $p = .05$
Med Ch	12	16		$X^2 = 0.25$, $p = .62$

Notes: Hypertension = According to ICD 10 as measured on the day of data acquisition. HIS = Hachinski ischemic score, Med BP = Number of persons taking medication against hypertension, Med D = Number of persons taking medication against diabetes, Med Ch = Number of persons taking medication against hypercholesterolemia

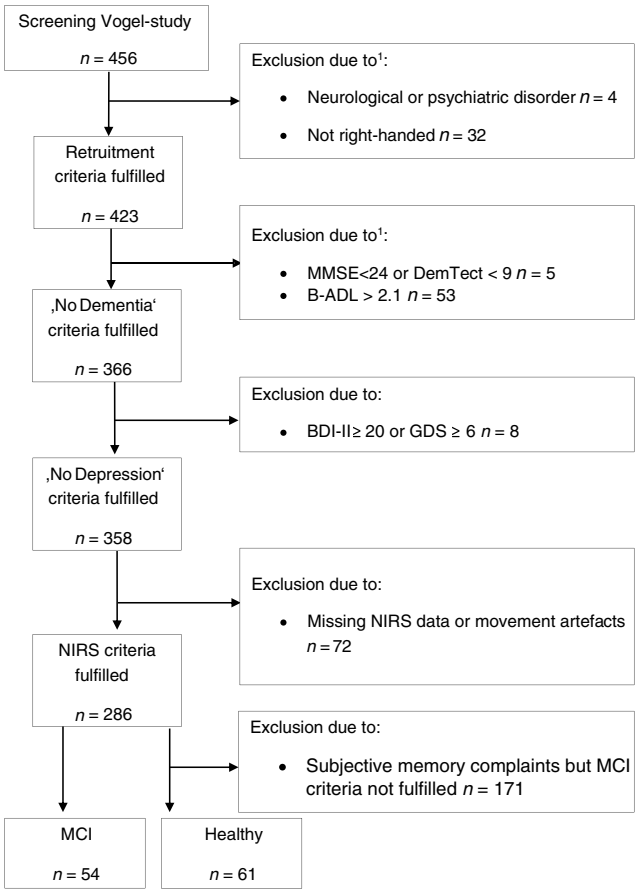

Fig. 1 Flow-Chart for the exclusion criteria of the elderly healthy as well as MCI participants from the Vogel-study sample. MMSE = Mini-Mental State Examination, BDI-II = Beck´s Depression Inventory-II, GDS = Geriatric Depression Scale, NIRS = near infrared spectroscopy, MCI = mild cognitive impairment.[1] = Some participants were excluded due to more than one reason

Hospital Würzburg. Both studies were approved by the Ethics Committee of the University Hospital Würzburg and were in accordance to the declaration of Helsinki. Written informed consent was given by all participants.

The elderly participants were selected from the larger collective of the VOGEL-study that contained at that time point 456 subjects (see Fig. 1 for a Flow-Chart). All participants of this study undergo thoroughly neuropsychological and psychiatric testing. Neuropsychological testing included three different domains: Memory functioning (Verbal learning and Memory Test (VLMT) and Wechsler Memory Scale (WMS-R)), executive functioning (Regensburger Word Fluency Test (RWT) and Rey Complex Figure Test (CFT)) and the Test of Attentional Performance (TAP, subtests: Incompatibility, Go/NoGo, Alertness and Divided Attention, for details see Polak et al. (2017)). Only right-handed subjects who did not suffer from any neurological or psychiatric disorders were included in the analysis. Furthermore subjects had to score above 8 in the DemTect and above 23 in the Mini-Mental State Examination (MMSE) to exclude dementia (Folstein et al. 1975; Kalbe et al. 2004). Subjects had to score below 2.1 points in the Bayer Activities of Daily Living Scale (Erzigkeit et al. 2001), indicating they had no impairment in their everyday life. To exclude the influence of severe depressive symptoms on cognitive performance and functional imaging subjects with ≥ 20 points in the Beck's Depression Inventory II and ≥ 6 points in the Geriatric Depression Scale were excluded from the analysis (Beck et al. 1996; Gauggel and Birkner 1999; Hautzinger et al. 2006; Yesavage et al. 1982). To be classified as MCI, subjects had additionally to perform below a t-score of 37.1 or a percentile of 9.85 in one outcome variable of the neuropsychological tests mentioned. All MCI criteria were based on recommendations of Portet et al. (2006), summarized the criteria were a subjective as well as objective cognitive impairment, no medium or severe depression, no dementia and no impairment in their everyday life. In a last step subjects showing movement artefacts or missing NIRS data in single channels were excluded. From the remaining group (n = 286) we identified a group of 61 healthy subjects without any cognitive complaints or impairment and a group of 54 subjects with MCI according to the criteria introduced by Portet et al. (2006). The remaining 171

subjects did report on subjective memory complaints but did not fulfill the MCI criteria. To minimize the influence of memory impairment mainly based on vascular reasons the Hachinski ischemic score (HIS) was obtained for all subjects of the VOGEL study (Hachinski, Iliff, Zilhka, & et al., 1975). All of them scored below 4 points that are suggested as the cutoff for potentially Alzheimer's disease by Rosen et al. (1980). The two elderly groups did not differ in their HIS. Medication status in reference to high blood pressure, diabetes and hypercholesterolemia did not differ between the two elderly groups (see Table1), although there was a trend for more subjects taking diabetes medication in the MCI group. As consequence medication status was not used as a covariate in the analysis of low frequency oscillations.

Paradigm and NIRS measurement

Older subjects underwent the NIRS measurement including five subtasks as part of the VOGEL-study (frontal and parietal rest measurement, a trail making test, a verbal fluency test and a test for angle discrimination). Younger subjects concluded three NIRS tasks as a control group of the WAS project (frontal rest measurement, a trail making test and a verbal fluency test). The tasks for the analysis of LFOs consisted of a 5 min resting period without any cognitive paradigm. Subjects were sitting in a sound-attenuated booth. They were instructed to keep their eyes closed and avoid any movement or active cognition. The lights were turned off. NIRS data were recorded using an ETG-4000 Optical Topography System (Hitachi Medical Co., Tokyo, Japan) employing two ranges of wavelengths (695 ± 20 and 830 ± 20 nm). Resting data were acquired separately for the frontal and the parietal cortex. For the frontal measurement a probe set of 3×11 optodes (17 laser emitters and 16 detectors, resulting in 52 channels) was placed on the forehead of the participants. The middle optode of the lowest row (detector 26) was located above the position Fpz of the international 10–20 system (Jasper 1958). The probe set covered frontal and temporal regions. For the parietal measurement a probe set consisting of two 3×5 optode arrays (8 laser emitters and 7 light detectors each, resulting in 2×22 channels) was placed on participants' back of the head. The two arrays were tied together to form one big probe set. The middle of the probe set was located above the position Pz of the international 10–20 system. Thus channels covered mainly parietal but also occipital and primary sensorimotor regions. NIRS data were recorded with a sampling rate of 10 Hz. The implemented ETG software calculated relative changes of oxygenated and deoxygenated hemoglobin according to a modified Beer–Lambert law (Obrig and Villringer 2003). As frequency oscillations were the focus of the analyses no moving average was employed.

Data analysis

All analyses were conducted using IBM SPSS Statistics 23 (SPSS Inc., Chicago, Ill., USA) and Matlab software (Version 7; MathWorks Inc., Natick, Mass., USA). The raw NIRS data did not underwent any filter or artefact correction algorithm before the analysis. As subjects were not required to speak or work on any task, we expected artifacts due to movement and biting to be negligible. According to the analysis described by Schroeter et al. (2004) NIRS data underwent a fast Fourier transformation to calculate the power spectral density (PSD). PSD of the whole spectrum was normalized to 1 for each subject. All further analyses focused on low frequency oscillations (LFO) containing oscillations from 0.07 to 0.11 Hz (adapted from Schroeter et al. (2004)). In this frequency range, Schroeter et al. (2004) detected statistical differences between younger and elderly subjects. LFO were examined separately for oxygenated and deoxygenated hemoglobin. Analyses of variance (ANOVA) and student t-tests were used to investigate the influence of age and cognitive status on LFO.

To minimize the disadvantage of multiple testing six regions of interest (ROI) were defined for the frontal probe set according to Müller et al. (2014). For both hemispheres of the frontal lobe there was a ventral, a medial and a lateral ROI. The ventral ROI included 6 channels each and the medial ROI 5 channels each. For each dorsal ROI 4 channels were integrated. The averaged PSD in the six ROIs was used for the following ANOVAs and student t-tests. For the parietal probe set four ROIs were created for the left and right hemisphere (see Fig. 2) considering the probabilistic anatomical cranio-cerebral correlation via the 10–20 system introduced by Okamoto et al. (2004): Channels of the sensorimotor ROI (SM) covered sensorimotor regions (left: 4, 9, 13, 18, 22; right: 1, 5, 10, 14, 19), channels of the inferior ROI (INF) covered the inferior parietal cortex (left: 2, 3, 6, 7, 11, 12; right: 2, 3, 7, 8, 11, 12), channels of the superior ROI (SUP) covered the superior parietal cortex (left: 15, 16, 17, 20, 21; right: 15, 16, 17, 20, 21), channels of the occipital ROI (OP) covered occipital parietal regions (left: 1, 5, 10, 14, 19; right: 4, 9, 13, 18, 22). The averaged PSD in the eight ROIs was used for the following ANOVAs and student t-tests.

LFO were compared between healthy younger and elderly participants and MCI subjects for the frontal probe set and between healthy elderly and MCI subjects for the parietal probe set. There was no parietal data available for younger participants, as the study protocol of the WAS-project did not include parietal NIRS measurement. To assess a possible connection between the amount of LFO and cognitive performance, bivariate correlation coefficients were calculated between the mean amount of LFO in the frontal and the parietal probe set and outcome variables of the

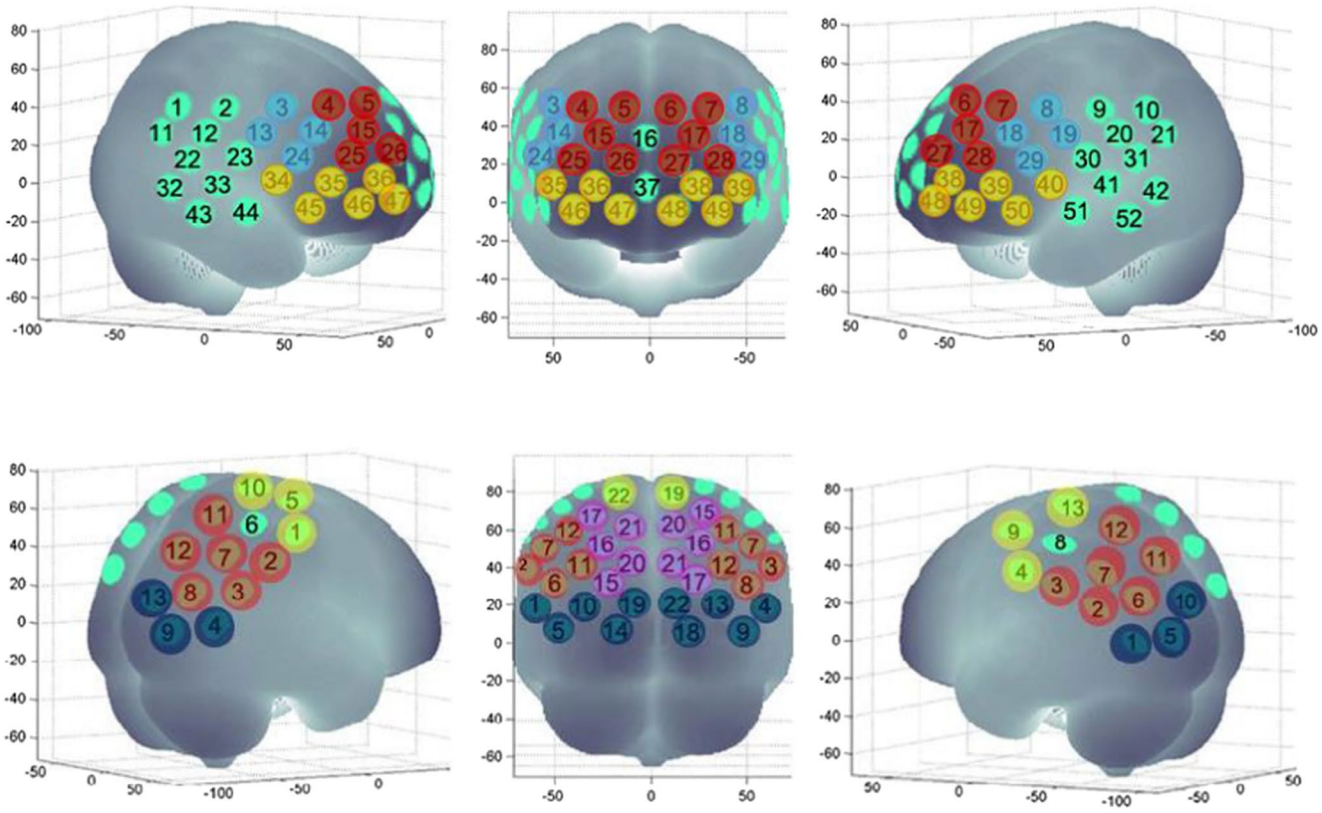

Fig. 2 Regions of Interest (ROI) for the frontal and parietal probe set. Circles represent NIRS channels. Frontal probe set: dark red: medial PFC, light blue: lateral PFC, dark yellow: ventral PFC. Parietal probe set: light yellow: sensorimotor ROI (SM), light red: inferior parietal ROI (INF), purple: superior parietal ROI (SUP), dark blue: occipital parietal ROI (OP)

neuropsychological tests (MMSE and DemTect: sum score, VLMT: 12 scores, RWT: 4 scores, CFT: 2 scores, WMS-R: 2 scores, TAP: 8 scores). The correlations were analyzed separately for [O_2Hb] and [HHb]. Due to multiple testing Holm-Bonferroni sequential selection was used for the correction of the α-level (Holm 1979) with a nominal α-level of 5%.

Results

Frontal probe set

Oxygenated hemoglobin

The 2×3×3 ANOVA for the mean PSD including the within factors hemisphere (left and right) and ROI (ventral, medial, lateral), and the between factor group (young, elderly, MCI) showed the significant main effects ROI ($F_{(2,270)} = 14.06$; $p < .001$) and group ($F_{(2,135)} = 12.79$; $p < .001$). Overall the NIRS data from younger participants displayed more LFOs than data from the elderly without cognitive complaints ($t_{82} = 3.08$; $p < .01$) and the MCI group ($t_{28.7} = 2.61$; $p < .05$; see Fig. 3, left side). The two elderly groups did not differ in their LFOs ($t_{112} = 0.19$; $p = .85$,). Regardless of group and hemisphere higher PSD could be found in the medial frontal cortex as compared to the ventral ($t_{138} = 4.51$; $p < .001$) and the lateral ROIs ($t_{138} = 6.10$; $p < .001$). No difference could be found between the ventral and the lateral ROI ($t_{138} = 0.12$; $p = .91$).

Deoxygenated hemoglobin

The 2×3×3 ANOVA for the mean PSD including the same factors as above showed the significant main effects ROI ($F_{(2,270)} = 43.94$; $p < .001$) and group ($F_{(2,135)} = 12.42$; $p < .001$), as well as the significant ROI x group interaction ($F_{(4,270)} = 7.3$; $p < .001$). The interaction effect was due to the fact that younger participants displayed more LFOs in the ventral (elderly: $t_{28.4} = 4.83$; $p < .001$; MCI: $t_{29.2} = 4.60$; $p < .001$) and in the lateral (elderly: $t_{24.77} = 2.10$; $p < .05$; MCI: $t_{25.2} = 2.15$; $p < .05$) ROI as compared to both other groups (see Fig. 3, right side). For the medial ROI this effect did not reach significance (elderly: $t_{26.4} = 1.94$; $p = .06$; MCI: $t_{27.6} = 1.74$; $p = .09$). Comparing the three ROIs in each group we observed the highest PSD in the ventral ROI in all groups. Apart from that each group showed distinct

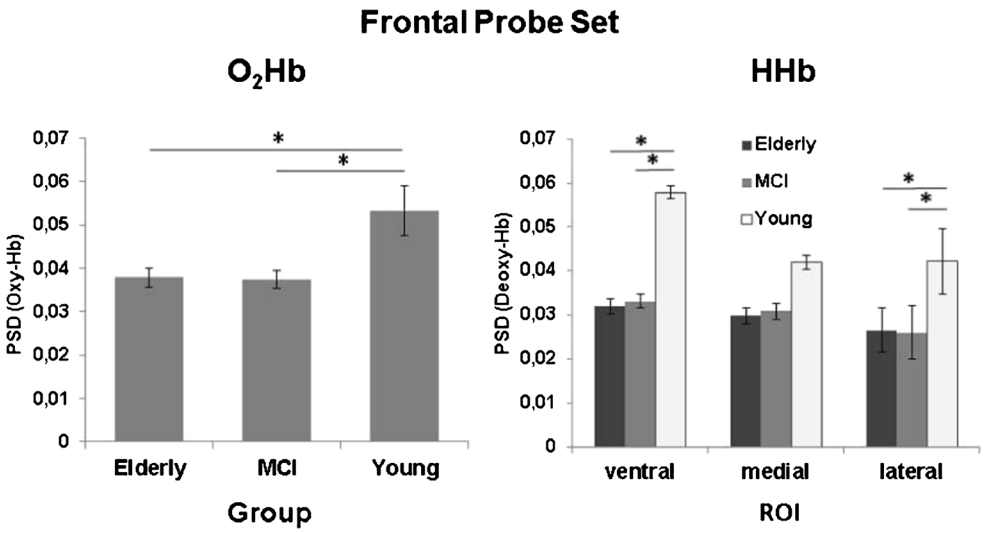

Fig. 3 Left side: Mean power spectral density of LFOs (0.7–0.11 Hz) observed for the three groups in [O_2Hb] for the frontal probe set. Right side: Mean power spectral density of LFOs (0.7–0.11 Hz) in the three ROIs of the frontal probe set observed in [HHb] separated by group. Error bars represent the standard error of the mean. * $p < .05$

differences between the ROIs. Older participants without cognitive complaints displayed highest PSD in the ventral ROI, less in the medial ($t_{60} = 2.10$; $p < .05$) and even less in the lateral ROI (ventral > lateral: $t_{60} = 4.25$; $p < .001$; medial > lateral: $t_{60} = 2.87$; $p < .01$). For subjects in the MCI group lowest PSD could be observed in the lateral ROI as well (ventral > lateral: $t_{53} = 5.99$; $p < .001$; medial > lateral: $t_{53} = 5.26$; $p < .001$) but there was no difference between the ventral and the medial ROI ($t_{53} = 1.79$; $p = .08$). In the young group no difference between the lateral and the medial ROI could be found ($t_{23} = 0.04$; $p = .97$) but both displayed less LFOs than the ventral ROI (ventral > medial: $t_{23} = 4.02$; $p < .01$; ventral > lateral: $t_{23} = 3.57$; $p < .01$).

Parietal probe set

Oxygenated hemoglobin

The 2 × 2 × 4 ANOVA with the between factor cognitive status (MCI and elderly control) and the within factors hemisphere (left and right) and ROI (SM, INF, SUP and OP) showed the significant main effects hemisphere ($F_{(1,112)} = 4.01$; $p < .05$), ROI ($F_{(3,336)} = 21.00$; $p < .001$) and cognitive status ($F_{(1,112)} = 4.62$; $p < .05$, see Fig. 3, left side) as well as the interaction ROI x hemisphere ($F_{(3,336)} = 3.60$; $p < .05$). Regardless of cognitive status more LFO could be observed in the occipital parietal ROI (OP) on the right side of the probe set as compared to the left ($t_{114} = 3.42$; $p < .01$). For the other three ROIs there was no difference between the hemispheres (SM: $t_{114} = 1.22$; $p = .23$; ROI INF: $t_{114} = -0.37$; $p = .71$; $t_{114} = 0.28$; $p = .78$). Subjects suffering from MCI overall displayed lower PSD in the parietal probe set than persons without any cognitive complains ($t_{98.4} = -2.2$; $p < .05$).

Deoxygenated hemoglobin

The 2 × 2 × 4 ANOVA with the same factors as above displayed the significant main effects hemisphere ($F_{(1,113)} = 6.31$; $p < .05$) and ROI ($F_{(3,336)} = 12.39$; $p < .001$) as well as the interactions hemisphere x ROI ($F_{(3,336)} = 8.81$; $p < .001$) and the three way interaction hemisphere x ROI x cognitive status ($F_{(3,336)} = 2.97$; $p < .05$). The three way interaction hemisphere x ROI x cognitive status displayed LFO differences between ROIs on the left side of the probe set for the MCI group (SM > SUP: $t_{53} = 2.29$; $p < .05$, INF > SUP: $t_{53} = 4.01$; $p < .001$, INF > OP: $t_{53} = 3.82$; $p < .001$) but not for persons without cognitive complaints. On the right side of the probe set both groups displayed the same pattern. The PSD in the SUP ROI was smaller than in the other ROIs (MCI group: SM > SUP: $t_{53} = 5.39$; $p < .001$, INF > SUP: $t_{53} = 3.81$; $p < .001$, OP > SUP: $t_{53} = 4.69$; $p < .001$; control group: SM > SUP: $t_{60} = 5.35$; $p < .001$, INF > SUP: $t_{60} = 4.11$; $p < .001$, OP > SUP: $t_{60} = 3.25$; $p < .01$, see Fig. 4, right side).

LFO correlations

Analysis showed a positive correlation between the median of the reaction time in the phasic alertness task of the TAP and oxy PSD in the parietal probe set in healthy elderly subjects ($r = .375$, $p < .01$). Persons displaying more LFO showed longer reaction times. This correlation could not be observed for the MCI group ($r = .05$, $p = .73$).

Discussion

As the first study on LFO using NIRS with multiple channels and across two cortical regions the present study could detect group differences between young and elderly subjects

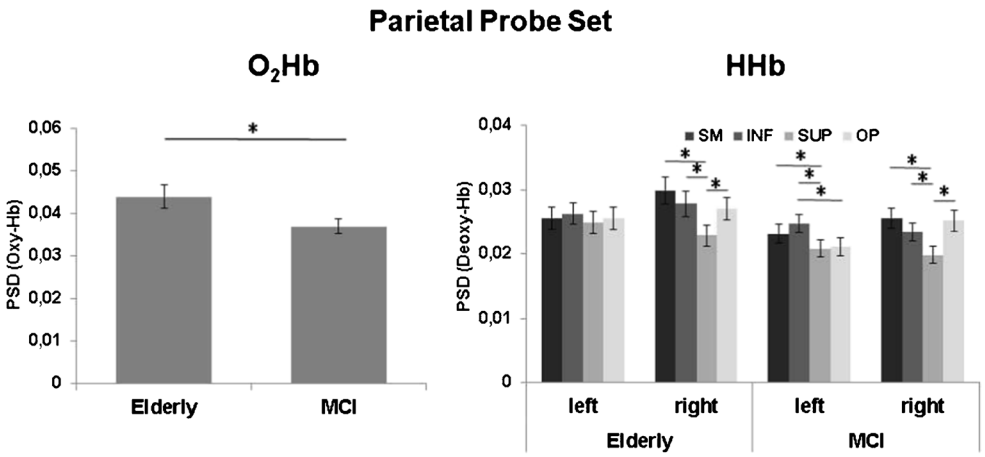

Fig. 4 Left side: Mean power spectral density of LFOs (0.7–0.11 Hz) observed for the two groups in [O_2Hb] for the parietal probe set. Right side: Mean power spectral density of LFOs (0.7–0.11 Hz) in the four ROIs of both sides of the parietal probe set observed in [HHb] separated by group. SM = sensory motor region, INF = inferior parietal cortex, SUP = superior parietal cortex, OP = occipital parietal region. Error bars represent the standard error of the mean. * $p < .05$

on the one hand and elderly and MCI subjects on the other hand in the frontal cortex. While the assessment of [O_2Hb] revealed just generally higher PSD in young participants, the results on [HHb] showed that this difference holds for the ventral and the lateral frontal ROI but not for the medial one. These findings are in accordance with Schroeter et al. (2004) who observed less LFO in elderly healthy subjects in the visual cortex during a checkerboard paradigm with NIRS. A decline of LFO in cortical regions might be a general sign of an aging cerebral microvasculature (Farkas and Luiten 2001).

The present results show no difference in PSD between elderly subjects with and without cognitive impairment in the frontal cortex. This observation is not consistent with the one of Zhao et al. (2014) who even detected increased oscillations in frontal regions in persons classified as MCI. They interpreted this finding as a sign of neural compensation. However it should be noted that our subjects in the MCI group were older (73.91 ± 1.8 yrs. vs. 65.11 ± 9.92 yrs.) and cognitively less impaired according to MMSE scores (28.81 ± 1.3 vs. 25.21 ± 2.24). It is possible that the amount of compensatory activity detectable via LFO decreases with age. Alternatively compensatory neural mechanisms might not be as pronounced in the present subjects as their performance is only slightly impaired. This interpretation would be in line with the finding that patients suffering from AD also show increased LFO in the frontal cortex (van Beek et al. 2012).

For the parietal cortex the present study revealed less LFO in the group classified as MCI as compared to healthy elderly controls. Again the analysis of [O_2Hb] found this as a main effect on the group level whereas the analysis of [HHb] showed a distinct pattern: While healthy elderly subjects displayed no differences between the four ROIs on the left side of the probe set the MCI group showed smaller PSD in the superior parietal cortex and the occipital parietal region as compared to the sensory motor region and the inferior parietal cortex. Zhao et al. (2014) also found decreased oscillations in the parietal cortex for their MCI group though on the right side. Reduced resting-state activation of the superior parietal cortex in MCI has already been reported in previous research (Sorg et al. 2007). A reduced glucose metabolism in this brain region even was shown to predict future memory decline and conversion to aMCI (Caselli et al. 2008). Reduced parietal task related activation has also been reported with NIRS for patients suffering from AD as compared to healthy elderly controls during a line orientation task (Zeller et al. 2010). The parietal cortex also is a region prone for the aggregation of plaques in the development of AD (Frisoni et al. 2009).

The present study found a correlation between the amount of LFO and outcome variables of neuropsychological tests. In healthy elderly subjects higher oxy PSD in the parietal probe set occurred alongside longer reaction times in the phasic alertness task of the TAP. Previous studies showed that generally healthy subjects display more LFO in the parietal cortex than aMCI subjects (Zhao et al. 2014). Thus this decrease of performance with increasing LFO could not be interpreted along the slope leading to MCI as in the frontal cortex. It could be suspected that the process of microvascular alteration with cognitive decline moves faster in the parietal cortex. At the time point of MCI manifestation the small vessels may already have succumbed to neural atrophy.

Though numerous studies have observed changes of LFO in aging and cognitive decline, the question remains how to interpret regional differences found with NIRS. In their combined NIRS/fMRI study Tong and Frederik (2010) come to the conclusion that LFO measured with NIRS indicate global cerebral blood flow and spontaneous fluctuations in central oxygenation. One has to argue that their six subjects were young (28.0 ± 4.69 yrs.) and healthy. A general decrease in LFO due to aging also falls in line with their results. Cerebral vessels become stiffer with age and the cerebral metabolism of oxygen and glucose declines (Farkas and Luiten 2001). Possibly disease related processes as the aggregation of plaques or tangles could interfere with this

global validity and create regional differences. If this was the case measuring LFO above just one cortical region would not be suited to detect signs of ongoing deterioration. Instead it might be crucial to monitor two or more cortical regions at once to develop an early detection method for MCI and/or AD. As the younger participants in the present study did not complete any parietal NIRS measurements no conclusions can be drawn regarding the change of LFO with age in this cortical area. Future studies should include the examination of LFO for multiple brain regions in multiple age groups.

It could be argued that we cannot totally exclude medication effects in our data. Previous studies found inconsistent results in that respect. While Schroeter et al. (2004) reported no influence of medication against hypertension in LFO, their later study (Schroeter et al. 2005) showed less LFO in [HHb] in connection with diabetes and statins. In the present study the two elderly groups did not differ significantly in their display of hypertension and the prescription of drugs against hypertension and hypercholesterolemia. There was a trend for MCI subjects taking more drugs against diabetes (MCI: 7 persons vs. healthy elderly: 2 persons). Their actual number however is very small and an additional analysis with diabetes medication as a covariate showed that no influence of medication could be seen in the present results.

Another limitation to our study could be the lack of blood pressure recordings during the NIRS measurement. In the 0-back version of their n-back task however Vermeij et al. (2014) observed a decline of LFO with age in [O_2Hb] and [HHb] as well as in peripheral blood pressure. This inactive condition of the n-back task could be –with limits- compared to the present rest measurement.

A significant difference in sex distribution between the groups could also put limitations to the findings of the present study. The young group consisted to a larger degree of female participants compared to the other groups. None of the studies on NIRS and LFO report on gender differences (Schroeter et al. 2005, 2004; Vermeij et al. 2014).Nevertheless future studies should consider this possibility.

In contrast to other studies using NIRS to examine LFO (Schroeter et al. 2005, 2004; Vermeij et al. 2014) the present study lacks an active task or even a visual stimulation. Measurements were solely taken during rest. The aim was to observe LFO in a setting that does not require any active part by the subject and to minimize the time required for measurement. For the broad use as an early detection method the measurement should be fast and easy. Changes in LFO due to cognitive load of stimulation could therefore not be investigated.

Summing up the current research, including our results, there seems to emerge a pattern in LFO changes when it comes to aging and cognitive decline. In healthy aging the amount of LFO detectable with functional imaging decreases, indicating the aging of the brain's microvasculature (Farkas and Luiten 2001; Schroeter et al. 2004). When it comes to MCI and AD studies found increased LFO in frontal and decreased LFO in parietal and temporal regions (van Beek et al. 2012; Zhao et al. 2014). The first is interpreted as a sign of compensatory processes the latter as an indication of disease related amyloid deposition and grey matter loss. The present study confirms this pattern except for the compensatory activity in the frontal cortex by MCI subjects. As indicated above, this might be due to our only slightly impaired MCI group. It is also possible that differences in frontal LFO need an active task to be detectable with NIRS. Further study is needed to understand the alterations of LFO with aging and disease and their underlying physiological processes. NIRS seems to be a suitable tool to examine large populations in this respect especially in longitudinal studies. As such it will be interesting to see if MCI subjects displaying cortical LFO alterations are more prone to converse to AD than subjects without alterations.

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Compliance with Ethical Standards

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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