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Age-related differences in the within-session trainability of hemodynamic parameters: a near-infrared spectroscopy–based neurofeedback study

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ABSTRACT

Neurofeedback studies revealed that the hemodynamic response as assessed with near-infrared spectroscopy (NIRS) can be voluntarily modulated. However, the hemodynamic response generally changes with age, and it remains unclear whether age-related differences in the hemodynamic response affect the trainability of brain signals. In the present study, $N = 24$ healthy young adults (mean age: 23 years; age range: 21–28 years) and $N = 19$ healthy older individuals (mean age: 69 years; age range: 60–84 years) performed one NIRS-based neurofeedback session. Half of all participants either tried to increase deoxygenated hemoglobin (deoxy-Hb) or decrease oxygenated hemoglobin over the inferior frontal gyrus (IFG) during imagery of swallowing movements. In addition, the hemodynamic response during motor imagery and execution of swallowing without real-time feedback was compared between groups. Young and older adults showed an opposite NIRS signal change during motor imagery, probably indicating a reduced movement inhibition ability in older individuals. Age-related differences in the trainability of the hemodynamic response during neurofeedback training were observed, too. Young participants were able to decrease oxygenated hemoglobin and increase deoxy-Hb over the bilateral IFG, whereas older participants were mainly able to increase deoxy-Hb over the left IFG. Our results provide evidence of age-related differences in the within-session trainability of the hemodynamic response as assessed with NIRS and have an impact on the application of NIRS-based real-time feedback.
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1. Introduction

Using neurofeedback (NF), brain signals are recorded, processed in real-time, and fed back to the NF user via visual, auditory, or tactile feedback. When receiving real-time feedback of brain signals, which are generally not perceivable, one can learn to modulate voluntarily these signals in a desired direction, which can lead to behavioral, cognitive, or motor improvements (Enriquez-Geppert et al., 2017; Gruzelier, 2014a; Kropotov, 2009; Strehl, 2014). In this context, activity of motor brain areas can be fed back to users in real-time while imagining specific movements. Thereby, NF users can learn to control voluntarily their activity in motor brain areas, leading to neuronal plasticity processes in the motor cortex and functional improvements (Decety, 1996; Faralli et al., 2013; Kober et al., 2014, 2015b; Mihara et al., 2013; Mihara and Miyai, 2016; Papoutsi et al., 2017; Pfurtscheller and Neuper, 1997; Ros et al., 2014; Weiskopf, 2012). This approach has mainly been used to restore hand and foot movements (Faralli et al., 2013; Kober et al., 2014; Mihara et al., 2013; Pfurtscheller and Neuper, 1997; Weiskopf, 2012; Wriessnegger et al., 2008). In recent near-infrared spectroscopy (NIRS) studies, we could show that motor imagery (MI) of swallowing is a useful mental strategy to modulated the hemodynamic response (oxygenated hemoglobin [oxy-Hb] and deoxygenated hemoglobin [deoxy-Hb]) in swallowing related brain areas (Kober et al., 2015b, 2018; Kober and Wood, 2014, 2018). This approach might be a valuable treatment for swallowing disorders or dysphagia in the future (Kober et al., 2015a,b; Kober and Wood, 2017a; Szynkiewicz et al., 2018; Yang et al., 2016).

Data availability: Data that support the findings of this study are available on request from the corresponding author (SEK) after contacting the Ethics Committee of the University of Graz (ethikkommission@uni-graz.at) for researchers who meet the criteria for access to confidential data. These ethical restrictions prohibit the authors from making the data set publicly available.

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During executing and imagining swallowing movements, the NIRS signal shows the strongest relative concentration changes over the inferior frontal gyrus (IFG) (Kober et al., 2015a,b, 2018; Kober and Wood, 2014, 2018; Sörös et al., 2009). Stroke patients with dysphagia symptoms show a more unilateral activation pattern during swallowing, especially an overactivation of the IFG in the affected hemisphere, whereas healthy individuals show a more bilateral activation of the IFG during swallowing (Kober et al., 2015a,b; Kober and Wood, 2014). These NIRS study results are in line with findings of prior functional magnetic resonance imaging studies supporting the importance of the IFG for the volitional swallowing process (Augustine, 1996; Ertekin and Aydogdu, 2003; Hamdy et al., 1999; Martin et al., 2001, 2001; Sörös et al., 2009). Although oxy- and deoxy-Hb increase during motor execution (ME) of swallowing in healthy young adults over the IFG, deoxy-Hb increases and oxy-Hb decreases during MI (Kober et al., 2015b; Kober and Wood, 2014). The observed decrease of oxy-Hb during MI of swallowing is interpreted as a sign of motor inhibition processes to avoid active swallowing during movement imagery (Ertekin, 2011; Gentili et al., 2013; Kober et al., 2015a,b; Kober and Wood, 2014; Matthews et al., 2008). In a recent study, we could demonstrate that only the natural course of the NIRS signal during MI of swallowing, which is an increase in deoxy-Hb and a decrease in oxy-Hb, can be reinforced by means of NIRS-based NF (Kober et al., 2018). Healthy young adults were able to voluntarily increase deoxy-Hb and decrease oxy-Hb but not the opposite direction when using MI of swallowing strategies during NF training (Kober et al., 2015b, 2018). In sum, these prior NIRS studies revealed cortical correlates of MI of swallowing and demonstrated the trainability of the NIRS signal by means of NF training (Kober et al., 2015a,b, 2018; Kober and Wood, 2014, 2018).

The trainability of the hemodynamic response when imagining swallowing movements has mainly been studied in healthy young individuals (Kober et al., 2015b, 2018; Kober and Wood, 2014, 2018). It is well known that the hemodynamic response generally changes with age. Older individuals show a smaller relative signal change in the hemodynamic response, for example, when performing cognitive tasks, movements, or movement imagery (Edlow et al., 2010; Gauthier et al., 2013; Kober and Wood, 2017b; Zich et al., 2017). Possible reasons for these age-related differences in the hemodynamic signal change might be differences in the baseline state, age-related differences in neuronal activity, or decreased vascular reactivity with age (Chen et al., 2011; Gauthier et al., 2013; Lu et al., 2011). Besides age-related differences in the hemodynamic response, age-related differences in cognitive functions are also evident. Age-related cognitive decline is mainly associated with decreased inhibition capacities. Inhibition is a central component of executive functions. It is defined as the ability to suppress irrelevant information and restrain inappropriate prepotent responses (Belanger et al., 2010; Bruin and Della Sala, 2018; Carver et al., 2009; Coxon et al., 2012; Hasher and Zacks, 1988; Kane and Engle, 2003; Zeintl and Kliegel, 2007). In a NIRS study investigating healthy young, middle-aged, and older individuals, we could demonstrate that age-related differences in the hemodynamic response are related to age-related differences in inhibition capacity (Kober and Wood, 2017b). Because of these age-related differences in the hemodynamic response of the brain as well as the age-related cognitive decline, the generalizability of findings in young individuals concerning the trainability of the hemodynamic response by means of NIRS-based NF training to older individuals, such as neurologic patients with dysphagia, is limited (Kober et al., 2015b, 2018; Kober and Wood, 2014, 2018).

The aim of the present study was to compare the trainability of hemodynamic parameters between healthy young and older individuals within one NF training session. In a first step, we performed a ME and MI offline task to investigate whether the NIRS signal change during executing and imagining swallowing movements is comparable between young and older individuals when no real-time feedback of brain signals is provided. In line with prior NIRS studies, we expect that deoxy-Hb should increase during both tasks, whereas oxy-Hb should increase during ME and decrease during MI in healthy young participants (Kober et al., 2015b, 2018; Kober and Wood, 2014). In older individuals, we expect a similar NIRS signal change during executing swallowing movements compared with young individuals (Kober et al., 2015a). Older individuals might show a smaller relative signal change in the hemodynamic response compared with young individuals, but the direction of the NIRS signal change (increase in oxy- and deoxy-Hb) should be the same (Edlow et al., 2010; Gauthier et al., 2013; Kober et al., 2015a; Kober and Wood, 2017b; Zich et al., 2017). In contrast, the NIRS signal change during imagining swallowing movements might differ between older and young individuals, as partly shown in 2 older single participants in a previous NIRS study by Kober et al. (2015a). In this study, 2 healthy older individuals showed an increase and no decrease in oxy-Hb during MI of swallowing (Kober et al., 2015a).

In a second step, we performed one NIRS-based NF training session with healthy young and older individuals to investigate directly the trainability of hemodynamic parameters in both age groups. Based on findings of our previous NIRS studies, we only trained the natural course of the NIRS signal when imagining swallowing movements over the IFG, which was observed in healthy young adults (Kober et al., 2015b, 2018). Hence, participants either tried to increase deoxy-Hb or to decrease oxy-Hb over the bilateral IFG during one session of NIRS-based NF training. In line with our previous findings, we expect that healthy young individuals should be able to increase voluntarily deoxy-Hb and decrease oxy-Hb during MI of swallowing. Because prior NIRS studies showed that relative concentration changes in the NIRS signal can be less pronounced in older individuals compared with younger individuals (Kober and Wood, 2017b), we hypothesize that this might also affect the trainability of the hemodynamic response in older participants. In addition, MI of swallowing leads to a decrease in oxy-Hb in healthy young adults, which might be a sign of motor inhibition (Ertekin, 2011; Gentili et al., 2013; Kober et al., 2015a,b; Kober and Wood, 2014; Matthews et al., 2008). Because inhibition capabilities also change with age, this might affect the NIRS signal and the ability to modulate the NIRS signal during NF training in older participants (Belanger et al., 2010; Kane and Engle, 2003; Kober and Wood, 2017b).

2. Materials and methods

2.1. Participants

Forty-three healthy adults took part in this study. $N = 24$ participants were between the age of 21 and 28 years (young group), and $N = 19$ participants were between the age of 60 and 84 years (older group). Half of all participants tried to increase voluntarily deoxy-Hb during NF training, whereas the other half tried to decrease voluntarily oxy-Hb. Participants of each age group were randomly assigned to the experimental conditions. Sample size, age, and gender ratio per group are depicted in Table 1. Preliminary analysis revealed no gender effects. Participants did not know in which group they were in nor did they know about this group design. All participants gave written informed consent. The participants had normal or corrected-to-normal vision and no history of neurological, psychiatric, respiratory, or swallowing disorders. The study was approved by the Ethics Committee of the University of Graz, Austria (reference number GZ. 39/25/63 ex 2013/14) and is

Table 1
Sample size, age (mean and SD), and gender ratio per group

Group characteristics	Young group		Older group	
	Increase deoxy-Hb	Decrease oxy-Hb	Increase deoxy-Hb	Decrease oxy-Hb
N	12	12	10	9
Age (y)	23.33 (1.67)	23.75 (2.01)	68.70 (5.56)	67.22 (7.12)
Males/females	5/7	2/10	4/6	3/6

Key: deoxy-Hb, deoxygenated hemoglobin; oxy-Hb, oxygenated hemoglobin.

in accordance with the ethical standards of the Declaration of Helsinki.

The present sample size is comparable to the sample size of prior NIRS studies that investigated ME and MI of swallowing during offline measurements and NIRS-based NF training studies using MI of swallowing as mental strategy in young individuals (Kober et al., 2015b, 2018; Kober and Wood, 2014). These prior studies found large effects (e.g., $f > 0.80$ [Kober et al., 2015b, 2018; Kober and Wood, 2014]). With our sample size, we can reveal such large effects (please also see reported η^2 values in the Section 3). With our design, we reach a sufficient post hoc power of >0.92 for the analysis of variance (ANOVA) models. Power calculations were performed with the software G*POWER (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/).

2.2. *Offline motor execution and motor imagery task*

Before the NF training, all participants performed an offline ME and MI task, in which they performed (10 ME trials) or imagined (10 MI trials) swallowing movements without real-time feedback of one's own brain activity in a randomized order. One trial consisted of a pause interval (variable duration 28–32 seconds), in which a fixation cross was presented on a screen and participants were instructed to relax and to avoid swallowing, and a task interval (either MI or ME, 15 seconds), in which participants either saw a "V" (shortcut for the German word "Vorstellen," imagine) or an "A" (shortcut for the German word "Ausführen," execute) on a screen. This offline task was also used in previous NIRS studies investigating cortical correlates of ME/MI of swallowing (Kober et al., 2015a,b, 2018; Kober and Wood, 2014, 2018). During MI, participants should imagine how it feels to swallow (kinesthetic imagery; Neuper et al., 2005) as long as the trial lasted. During ME, participants should swallow saliva as long as the trial lasted. Possible muscle activity during MI of swallowing was controlled by visual inspection of the experimenter during the measurement. Before the start of this offline task, participants were shortly trained in the MI and ME tasks. Therefore, one practice trial of the ME and one practice trial of the MI task were presented with the correct timing (including the pause intervals in between) and participants should already perform the tasks as required during the subsequent NIRS measurement. The whole ME/MI offline task took 15 minutes.

2.3. *NIRS-based neurofeedback training*

Within one NIRS-based NF training session, participants either tried to increase deoxy-Hb or decrease oxy-Hb voluntarily while receiving visual feedback of the training parameter (either deoxy- or oxy-Hb). They performed 20 feedback trials with a variable length of 17–23 seconds (Kober et al., 2015b, 2018). Between the feedback trials, there was a pause interval of 30 seconds. Auditory commands indicated the start and the stop of the feedback trials. During the whole NF training session, changes in oxy- and deoxy-Hb were depicted continuously on a three-dimensional head model (MATLAB–The MathWorks) over the measured brain regions (Fig. 1), respectively. For online feedback, the software NIRStar 13.1 (NIRx Medizintechnik GmbH, Berlin, Germany) was used. The signal was sampled with 7.81 Hz, and a low-pass filter of 0.90 Hz was used. To smoothen the feedback signal, a moving average of 4 samples was used. During the feedback trials, participants should modulate voluntarily the color of the bilateral IFG by imagining swallowing movements (color changes from blue over green to red). In Fig. 1B, red rectangles indicate the location of the bilateral IFG in the feedback screen. During the NF training, these red rectangles were not shown. However, participants were instructed to modulate the color of these brain regions before the start of the NF training. Depending on the location of the relative concentration changes in oxy- or deoxy-Hb, the size of the color blobs on the three-dimensional head model could also vary. Participants who tried to increase deoxy-Hb were instructed to increase the reddish color on the head during imagining swallowing (Fig. 1A), whereas participants who tried to decrease oxy-Hb should increase the blueish color on the feedback head (Fig. 1B). During the pause interval, the colors on the head should turn green (Kober et al., 2018). Participants constantly received feedback about concentration changes in oxy-/deoxy-Hb during the pause interval. The participants were instructed to try to reach a green color during the pause. A constant green color indicated that oxy- or deoxy-Hb did not change during the pause. If the participants increased or decreased oxy-/deoxy-Hb during the pause interval, the color of the head changed in a comparable way as during the feedback trials. The whole NF training task took about 17 minutes.

After the NF training, participants indicated on a visual analog scale (VAS) ranging from 0 to 100 how well they think that they have succeeded in the MI task (0 = not succeeded at all; 100 = succeeded perfectly) and how easy/difficult the MI task has been (0 = very difficult; 100 = very easy). In addition, participants were instructed to imagine how it feels to swallow because there is evidence that kinesthetic MI leads to a stronger activation of motor brain areas than pure visual imagination (Neuper et al., 2005). To assess whether participants used a kinesthetic MI strategy rather than a visual strategy, participants had to rate on a VAS ranging from 0 to 100 whether they have imagined the MI swallowing task visually (0) or kinesthetically (how it feels to swallow, 100) after the NF task.

2.4. *NIRS recordings and analysis*

To assess the NIRS signal, we used the NIRSport 88 system from NIRx Medical Technologies (Glen Head, NY, USA) consisting of 8 photodetectors and 8 light emitters resulting in a total of 20 channels. The 20 NIRS channels were placed over bilateral areas including the dorsolateral prefrontal cortex, IFG, Broca's area, premotor, and supplementary motor cortex (Fig. 1C). In accordance with prior NIRS studies showing that MI and ME of swallowing is associated with the strongest NIRS signal change over the bilateral IFG (Kober et al., 2015a,b, 2018; Kober and Wood, 2014), for statistical analysis, we only analyzed channels over the bilateral IFG (the IFG was covered by channels 9, 10, 19, and 20, Fig. 1C, Kober et al., 2018). The NIRS optodes were integrated in a cap, which also contained the 10–20 electrode placement locations conventionally used for electroencephalography measurements (Jasper, 1958). The cap was attached to the participants' head in accordance with this 10–20 placement system. The sampling rate was 7.81 Hz, and the distance between the optodes was 3 cm. Because the NIRSport 88 system is a continuous wave system as most NIRS systems are, oxy- and deoxy-Hb cannot be determined absolutely (Scholkmann et al., 2014). Hence, relative concentration changes in oxy- and deoxy-Hb are quantified with this method.

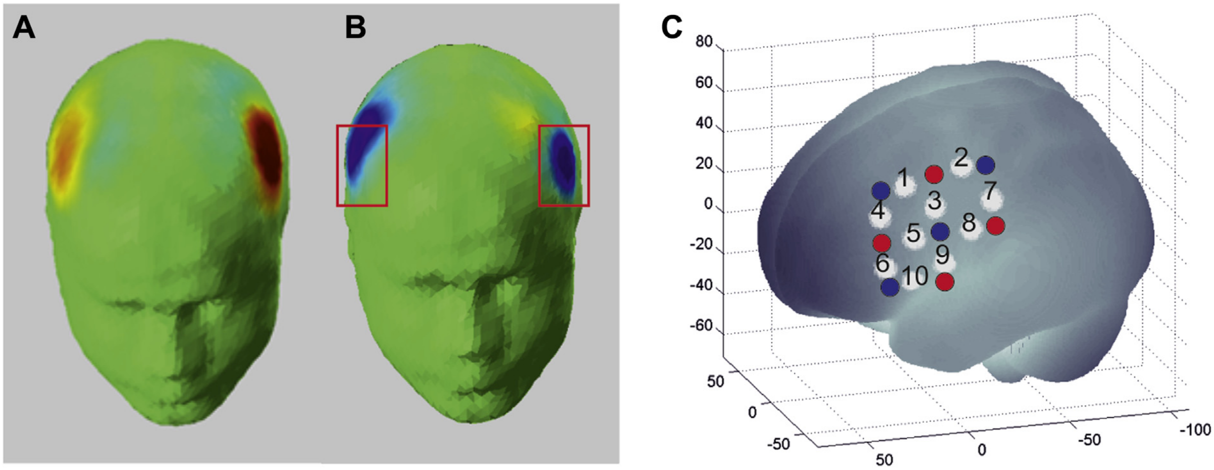

Fig. 1. (A) Example of the feedback screen (three-dimensional head model), when participants should increase deoxy-Hb by increasing the reddish color of the bilateral feedback regions, and (B) when participants should decrease oxy-Hb by increasing the blueish color of the bilateral feedback regions (marked with red rectangles). (C) Projections of 10 of the 20 NIRS channel positions (white points) on the cortical surface over the left hemisphere. Channel numbers 9 and 10 corresponded to the left IFG. Positions of NIRS emitters (red points) and detectors (blue points) are additionally marked. NIRS positions are overlaid on an MNI-152 compatible canonical brain that is optimized for NIRS analysis according to a procedure of Singh et al. (2005). Abbreviations: deoxy-Hb = deoxygenated hemoglobin; oxy-Hb = oxygenated hemoglobin; NIRS = near-infrared spectroscopy; IFG = inferior frontal gyrus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

For data analysis, relative concentration changes in oxy-Hb and deoxy-Hb were investigated. Data preprocessing included an artifact correction (criterion for rejection: amplitude of Hb-signal > +/−3 SD; visual inspection by a trained expert in NIRS data analysis), band-pass filtering (0.01 Hz high-pass filter, 0.90 Hz low-pass filter), and baseline correction (5 seconds baseline interval before the tasks, seconds −5 to 0). Time courses of the NIRS signal change were averaged task-related. For statistical analysis of the NF training data, the recorded signals were split up in 5 blocks (B1–B5) of 4 trials: the NIRS signal of the first 4 feedback trials (trial 1–4: B1), trial number 5–8 (B2), trials 9–12 (B3), trials 13–16 (B4), and the last 4 trials (trial 17–20: B5) were averaged, respectively. For statistical comparisons, oxy-Hb and deoxy-Hb were averaged for the time interval 10–15 seconds after task onset (NF task and ME/MI offline task).

3. Results

3.1. Motor execution and imagery of swallowing during offline measurement

To analyze possible group differences in the hemodynamic response during offline ME and MI, ANOVA models with the within-subject factor hemisphere (left vs. right IFG) and the between-subject factors age (young vs. old) and feedback parameter (increase deoxy-Hb vs. decrease oxy-Hb) were calculated, separately for the dependent variable oxy-Hb during ME, deoxy-Hb during ME, oxy-Hb during MI, and deoxy-Hb during MI.

The ANOVA for the dependent variable oxy-Hb during ME revealed a significant main effect of hemisphere ($F(1,39) = 4.60$, $p < 0.05$, $\eta^2 = 0.11$). Oxy-Hb increased stronger over the left IFG ($M = 0.20$ m(mol/l)*mm, $SE = 0.030$) than over the right IFG ($M = 0.16$ m(mol/l)*mm, $SE = 0.022$) during ME of swallowing in all groups. Although descriptively the increase in oxy-Hb during ME was stronger in young than in older participants (Fig. 2), the group differences were statistically not significant ($F(1,39) = 0.31$, *ns.*).

No significant effects were revealed by the ANOVA for the dependent variable deoxy-Hb during ME.

During MI of swallowing, relative concentration changes in oxy-Hb differed significantly between age groups ($F(1,39) = 21.18$, $p < 0.01$, $\eta^2 = 0.36$). Older individuals showed an increase in oxy-Hb ($M = 0.034$ m(mol/l)*mm, $SE = 0.008$), whereas younger individuals showed a decrease in oxy-Hb ($M = -0.014$ m(mol/l)*mm, $SE = 0.007$) during MI of swallowing (Fig. 2).

Age-related differences were also evident in deoxy-Hb signal changes during MI of swallowing ($F(1,39) = 5.57$, $p < 0.05$, $\eta^2 = 0.13$). Older individuals showed a decrease in deoxy-Hb ($M = -0.006$ m(mol/l)*mm, $SE = 0.005$), whereas younger individuals showed a relative increase in deoxy-Hb ($M = 0.009$ m(mol/l)*mm, $SE = 0.004$) during MI of swallowing (Fig. 2).

NIRS signal changes during the offline ME and MI swallowing tasks are shown in Fig. 2 separately for older and younger individuals.

3.2. Neurofeedback training performance

To analyze changes in the NIRS signal over the NF training course, regression analyses were performed (predictor variable = block number B1–B5; dependent variable = average of oxy-Hb or deoxy-Hb for second 10–15 after start of the NF task). The resulting regression slopes were considered as indicators of NF performance. For the deoxy-Hb groups, successful NF performance (responder) was assumed when the regression slope was >0. For the oxy-Hb groups, successful NF performance (responder) was assumed when the regression slope was <0. The NF training performance per group and the regression slopes are illustrated in Fig. 3. Table 2 summarizes the number of responders and nonresponders per age and training group, separately for the regression slopes of the NIRS signal over the left and right IFG. Note that the number of responders and nonresponders as illustrated in Table 2 is a descriptive presentation of the data. A statistical comparison of the regression slopes between groups was subsequently performed using ANOVA models.

The regression slopes were compared between groups using ANOVA models with the within-subject factor hemisphere (left vs. right IFG) and the between-subject factors age (young vs. old) and feedback parameter (increase deoxy-Hb vs. decrease oxy-Hb) separately for the dependent variables regression slopes of oxy-Hb and deoxy-Hb.

The ANOVA for the dependent variable oxy-Hb slope revealed a significant 3-way interaction hemisphere * feedback parameter

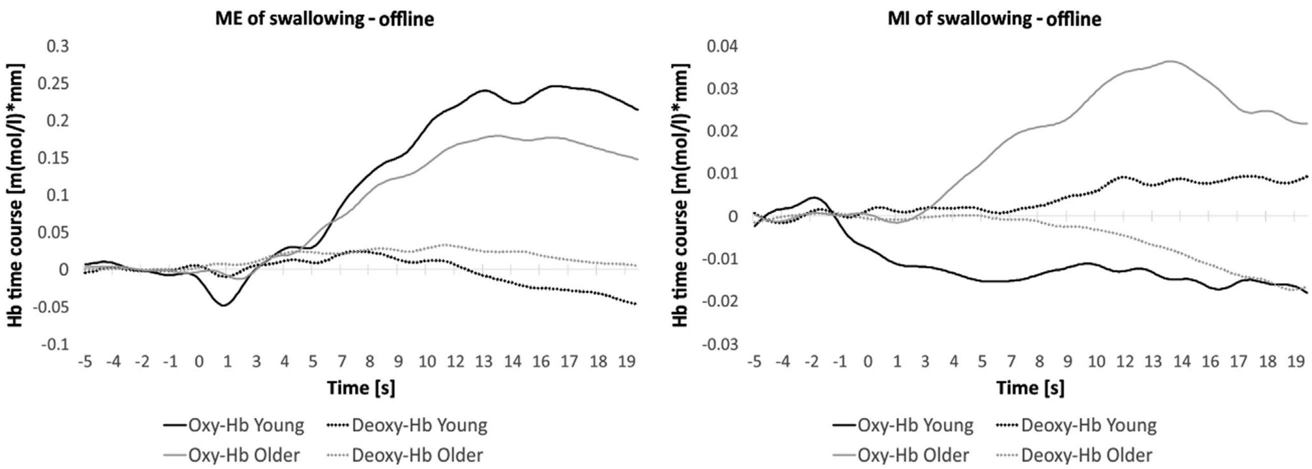

Fig. 2. NIRS time course during offline measurements. Relative concentration changes in oxy- and deoxy-Hb during motor execution (ME, left panel) and motor imagery (MI, right panel) of swallowing when no real-time feedback was provided, presented separately for younger and older participants. Note that the MI/ME swallowing task started at second 0. Abbreviations: deoxy-Hb = deoxygenated hemoglobin; oxy-Hb = oxygenated hemoglobin; NIRS = near-infrared spectroscopy.

* age (F (1,39) = 3.87, $p = 0.05$, $\eta^2 = 0.09$). Posttests revealed that young participants who trained to decrease oxy-Hb showed a stronger negative slope than older individuals who trained to decrease oxy-Hb over the right IFG (t (17.91) = 2.11, $p < 0.05$) (Fig. 4).

For the dependent variable deoxy-Hb slope, the ANOVA revealed a significant 2-way interaction effect of hemisphere * age (F(1,39) = 4.10, $p < 0.05$, $\eta^2 = 0.10$). Posttests revealed that younger participants showed a stronger positive slope ($M = 0.010$, $SE = 0.004$) than older participants ($M = -0.003$, $SE = 0.004$) over the right hemisphere (t (41) = −2.21, $p < 0.05$). Although the 3-way interaction effect of hemisphere * feedback parameter * age was not significant, for better comparability of the results, the means and standard errors for this effect are depicted in Fig. 5.

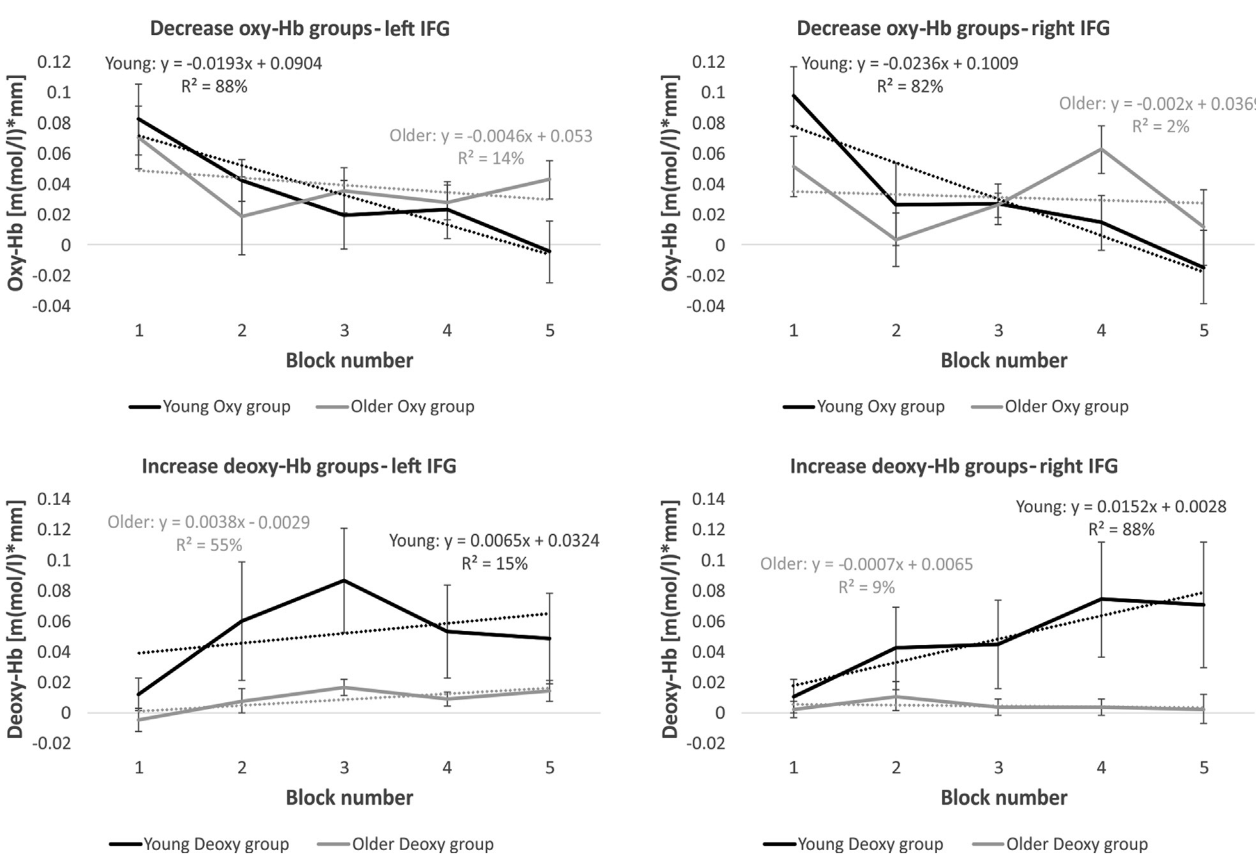

Fig. 3. Neurofeedback training performance (means and *SE* in oxy-/deoxy-Hb) for the decrease oxy-Hb groups (upper panels) and the increase deoxy-Hb groups (lower panels), presented separately for the different age groups (black lines: young groups; gray lines: older groups) and the left IFG (left panels) and right IFG (right panels). The results of the regression analysis (predictor variable = block number B1-B5; dependent variable = average of oxy-Hb or deoxy-Hb sec 10–15) per group are presented as well. Abbreviations: deoxy-Hb = deoxygenated hemoglobin; oxy-Hb = oxygenated hemoglobin; IFG = inferior frontal gyrus.

Table 2
Neurofeedback performance: absolute number (and percentage) of responders and non-responders per group, presented separately for the regression slopes of the NIRS signal change over the left and right IFG

Neurofeedback performance	Young group				Older group			
	Increase deoxy-Hb		Decrease oxy-Hb		Increase deoxy-Hb		Decrease oxy-Hb	
	Left IFG	Right IFG	Left IFG	Right IFG	Left IFG	Right IFG	Left IFG	Right IFG
Responders	8 (66.67%)	8 (66.67%)	8 (66.67%)	7 (58.33%)	8 (80%)	6 (60%)	4 (44.44%)	4 (44.44%)
Non-Responders	4 (33.33%)	4 (33.33%)	4 (33.33%)	5 (41.67%)	2 (20%)	4 (40%)	5 (55.56%)	5 (55.56%)

Key: deoxy-Hb, deoxygenated hemoglobin; IFG = inferior frontal gyrus; oxy-Hb, oxygenated hemoglobin.

The NIRS time courses for the different training and age groups are depicted in Fig. 6.

3.3. Subjective ratings concerning MI ability

To investigate whether groups differed in their ability to imagine swallowing movements, participants indicated on a VAS how well they think that they have succeeded in the MI task and how easy/difficult the MI task has been. An ANOVA with the between-subject factors age (young vs. old) and feedback parameter (increase deoxy-Hb vs. decrease oxy-Hb) revealed no significant group differences for these 2 VAS ratings. In addition, we asked the participants whether they have used a visual or kinesthetic mental strategy during MI of swallowing. Again, an ANOVA model with the between-subject factors age (young vs. old) and feedback parameter (increase deoxy-Hb vs. decrease oxy-Hb) revealed no significant group differences for this mental strategy rating. The results of these VAS ratings are depicted in Table 3. Hence, participants rated their ability to imagine swallowing in a comparable way.

4. Discussion

In the present study, we investigated age-related differences in the within-session trainability of the hemodynamic response of the brain as assessed with NIRS. Therefore, healthy young and older participants performed one NIRS-based NF training session in which they either tried to increase deoxy-Hb or decrease oxy-Hb while imagining swallowing movements. The time course of the NIRS signal differed between young and older individuals, especially during MI. Age-related differences in the within-session trainability of the NIRS signal were observed, too. In the following, these results are discussed in ore detail.

Executing swallowing movements revealed no prominent age-related differences in the hemodynamic response. As one can see in Fig. 2, the relative signal increase in oxy-Hb during ME was more pronounced in young than in older participants. However, this difference did not reach statistical significance. This is in line with an NIRS study by Zich et al. (2017), in which healthy young and older individuals executed and imagined hand movements. The authors also found a numerically stronger NIRS signal change (especially for oxy-Hb values) during ME of hand movements in young compared with older participants although these age-related differences did not reach statistical significance (Zich et al., 2017). Generally, the time course of the NIRS signal during executing swallowing movements observed in both age groups of the present study is comparable to the NIRS time course found in previous studies investigating healthy young adults (Kober et al., 2015b; Kober and Wood, 2014, 2018).

During ME, oxy-Hb showed a stronger increase over the left compared with the right IFG. This is in line with prior findings that swallowing saliva as in the present study leads to a stronger activation over the left hemisphere, whereas swallowing water generally leads to a more right lateralized activation focus (Kober and Wood, 2018; Sörös et al., 2009).

When imagining swallowing movements during the offline task without real-time feedback, the NIRS signal change differed fundamentally between age groups. Young individuals showed an increase in deoxy-Hb and a decrease in oxy-Hb, which is in line with previous findings (Kober et al., 2015b, 2018; Kober and Wood, 2014). This time course observed in healthy young adults was defined as natural course of the NIRS signal during MI of swallowing in former studies (Kober et al., 2015b, 2018). Healthy older individuals showed an NIRS signal change in the opposite direction. While deoxy-Hb decreased, oxy-Hb increased when imagining swallowing. This finding is in line with a previous patient study, investigating stroke patients with dysphagia, in which 2 single healthy older adults were assessed as controls (Kober et al., 2015a). These 2 healthy older controls showed a similar NIRS signal change to the older group of the present study, especially an increase in oxy-Hb during MI of swallowing (Kober et al., 2015a). Generally, a decrease in oxy-Hb during imagining swallowing compared with a rest period observed in young adults is explained by possible motor inhibition mechanisms (Gentili et al., 2013; Kober and Wood, 2014). Although participants should avoid active movements during MI, imagining movements contains motor execution programs for muscle contractions. These motor execution programs have to be blocked at some level of the motor system by inhibitory mechanisms, which might in turn lead to a decreased activation level in swallowing-related brain areas as indicated by decreases in oxy-Hb (Guillot et al., 2012; Kasess et al., 2008; Kober and Wood, 2014).

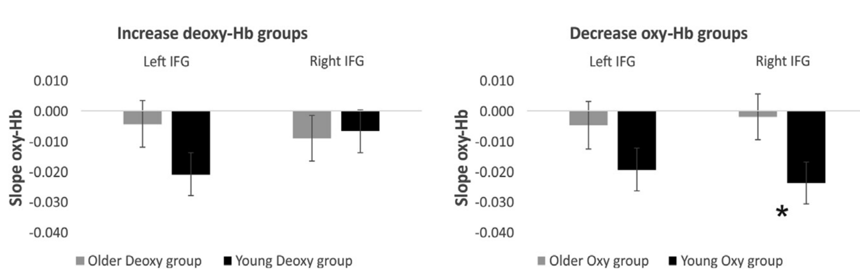

Fig. 4. Results (means and *SE*) of the ANOVA analysis for the dependent variable oxy-Hb slope: 3-way interaction effect of hemisphere * feedback parameter * age. Significant differences are marked with asterisks (*$p < 0.05$). Abbreviations: ANOVA = analysis of variance; deoxy-Hb = deoxygenated hemoglobin; oxy-Hb = oxygenated hemoglobin; IFG = inferior frontal gyrus.

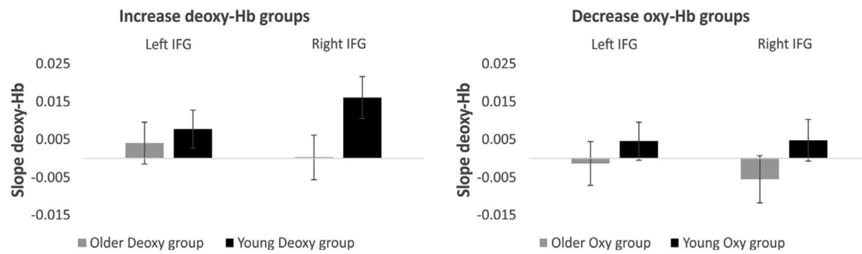

Fig. 5. Results (means and *SE*) of the ANOVA analysis for the dependent variable deoxy-Hb slope: 3-way interaction effect of hemisphere * feedback parameter * age. Abbreviations: ANOVA = analysis of variance; deoxy-Hb = deoxygenated hemoglobin; oxy-Hb = oxygenated hemoglobin; IFG = inferior frontal gyrus.

Because inhibitory control mechanism deteriorates with increasing age (Belanger et al., 2010; Bruin and Della Sala, 2018; Carver et al., 2009; Coxon et al., 2012; Hasher and Zacks, 1988; Kane and Engle, 2003; Kober and Wood, 2017b; Zeintl and Kliegel, 2007), the ability to inhibit or block motor execution programs involved in MI might be reduced in older individuals. Although the older group of the present study did not swallow actively during the MI task, which was checked by visual inspection, we cannot exclude that older participants produced micromovements during MI, which could not be detected by visual control. Such small movements of muscles involved in swallowing, for example, suprahyoid muscles, caused by an incomplete inhibition of the motor command might have led to the observed increase in oxy-Hb during MI in older individuals (Guillot et al., 2012). Prior studies in patients with brain lesions also showed diminished inhibitory control, which led to involuntarily movements while imaging motor actions (Guillot et al., 2012; Kober et al., 2015a). To investigate directly whether an incomplete motor inhibition in older individuals might be responsible for the increase in oxy-Hb during MI of swallowing in this age group, activity of muscles involved in swallowing has to be controlled by using, for instance, the electromyogram in future studies (Kober and Wood, 2014).

Structural age-related differences in the brain might be an alternative explanation for the observed age-related differences in the NIRS signal change during MI. Due to structural age-related differences in the brain, the amount of measured brain tissue might have been different between groups (Fjell and Walhovd, 2010). Using NIRS, it is possible to measure activity changes in the outer layer of the cortex, maximum 3–4 cm from the surface of the head (Villringer and Chance, 1997). The observed changes in the NIRS signal over the IFG during MI of swallowing might have been caused by activity changes in deeper brain areas, such as the insula, which is also strongly involved in the swallowing process (Hamdy et al., 1999; Humbert and Robbins, 2007; Kober and Wood, 2014; Liu et al., 2015; Martin et al., 2001; Sörös et al., 2009; Villringer and Chance, 1997). There is evidence that the insula plays a central role in self-regulation of one's own brain activity during NF, focusing attention on inner states and oneself, as necessary during MI (Emmert et al., 2016; Kober et al., 2017b; Ninaus et al., 2013, 2015; Wood et al., 2014). Due to changes in brain volume size with age (Fjell and Walhovd, 2010), activation of such deeper brain areas might be harder to measure with NIRS in older compared with young individuals (Augustine, 1996). Hence, involvement of deeper brain areas such as the insula during MI might be detectable in younger individuals by using NIRS but not in older individuals, leading to the observed age differences in the NIRS signal change during MI of swallowing.

Concerning the NF training performance, we could support prior findings that young participants were able to increase voluntarily deoxy-Hb and decrease oxy-Hb by imagining swallowing movements within one NF training session (Kober et al., 2015b, 2018). This underlines the within-session trainability of the hemodynamic response by reinforcing the natural course of the NIRS signal change (Kober et al., 2018). In the present investigation, we defined successful NF training performance as a linear change in brain activity within one NF training session such as in a previous NIRS study in healthy young individuals (Kober et al., 2018). Hence, the trainability of the hemodynamic response was defined as within-session changes in oxy- and deoxy-Hb in a desired direction. Generally, the question whether successful NF performance (and consequently the "trainability" of brain signals) is associated with within- or between-session changes in brain signals is a highly disputed question in the NF literature (Enriquez-Geppert et al., 2017; Gruzelier, 2014b). In the present study, we performed one NF training session and therefore we had to focus on within-session changes in the NIRS signal. In a previous NIRS-based NF training study, we performed 7 NF training sessions (Kober et al., 2015b). In this study, we found between-session changes in the NIRS signal in healthy young adults. However, in the study by Kober et al. (2015b) within-session changes of the hemodynamic response were not analyzed (Kober et al., 2015b). Gaining voluntary control over one's own brain activity by means of NF training and thereby being able to module voluntarily one's own brain activity in a desired direction does not necessarily depend on changes in baseline levels of brain activity of an NF user between sessions (Kober et al., 2015d, 2018). In the present investigation and in previous NF studies, we could successfully show that participants are able to modulate their brain activity voluntarily at a given time (within an NF training session) (Kober et al., 2015c,d, 2017a, 2017b, 2018). According to Dempster and Vernon (2009), focusing on within-session changes may be a more useful approach in identifying changes resulting from NF training (Dempster and Vernon, 2009).

In the present study, the proportion of responders and non-responders in young adults is comparable to other NF training studies. Generally, a third of potential NF users are not able to modulate their own brain activity in the desired direction (Allison and Neuper, 2010).

Older individuals were largely able to increase deoxy-Hb over the left hemisphere. However, young individuals showed a stronger linear increase in deoxy-Hb during NF training than older ones, especially over the right hemisphere. As one can see in Figures 3 and 6, there is more variability in the deoxy-Hb signal in young than in older participants over the course of the NF training session. Both age groups show a comparable increase in deoxy-Hb during the first NF training block (B1, Fig. 6). Between the second and the fifth blocks of the NF training (B2–B5), the amplitude of the deoxy-Hb signal increases constantly from block to block in young participants. In older participants, the deoxy-Hb signal change remained more or less stable over all 5 blocks. It only showed small increases in amplitude during the analyzed time window (10–15 seconds after task onset), leading to a linear increase when calculating regression analysis as well. This result might be related

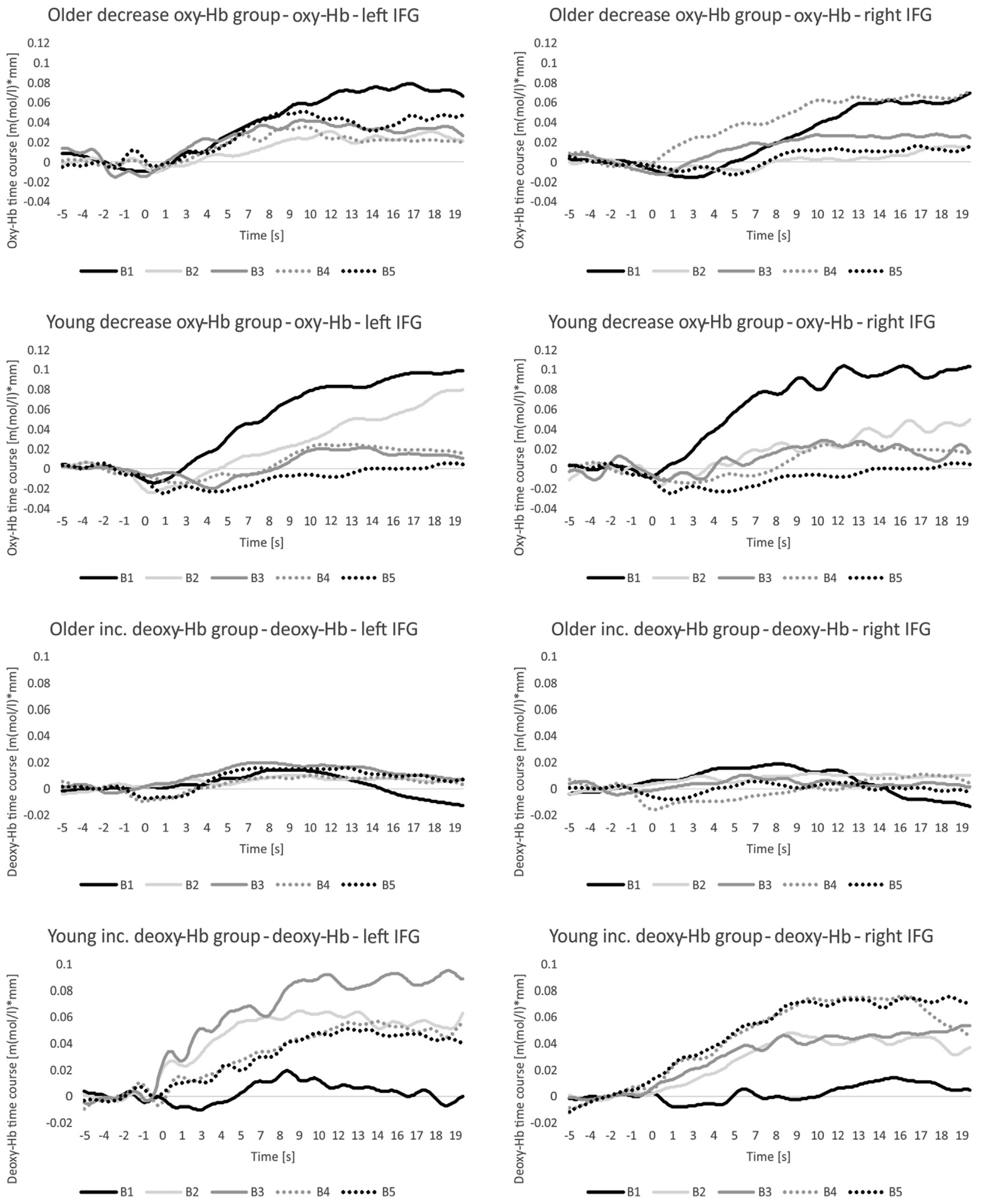

Fig. 6. NIRS time course during NF training per group. Relative concentration changes in oxy- and deoxy-Hb during NF training, presented separately for the 5 feedback blocks (B1-B5), the left and right IFG, and for the different feedback groups. Note that the NF training task started at second 0. Abbreviations: deoxy-Hb = deoxygenated hemoglobin; oxy-Hb = oxygenated hemoglobin; IFG = inferior frontal gyrus; NIRS = near-infrared spectroscopy; NF = neurofeedback.

Table 3
Results of the VAS ratings (mean and *SE*, ranging from 0–100), presented separately for the different groups

Results of subjective ratings concerning MI ability	Young group		Older group	
	Increase deoxy-Hb	Decrease oxy-Hb	Increase deoxy-Hb	Decrease oxy-Hb
VAS 1: How well did you succeed in the MI task?	60.17 (9.68)	50.42 (9.68)	69.26 (10.61)	50.75 (11.18)
VAS 2: How easy/difficult was the MI task?	55.33 (9.62)	55.58 (9.62)	66.63 (10.54)	59.29 (11.11)
VAS 3: Did you imagine the MI task visually or did you imagine how it feels to swallow?	70.62 (7.71)	69.83 (7.71)	70.63 (8.44)	56.02 (8.90)

Key: deoxy-Hb, deoxygenated hemoglobin; MI = motor imagery; oxy-Hb, oxygenated hemoglobin; VAS = visual analog scale.

to the observation that older individuals show a reduced adaptation of the hemodynamic response as compared with young people (Grill-Spector et al., 2006; Kober and Wood, 2017b; Miyakoshi et al., 2012). Hence, young participants show a higher adaptation or “flexibility” of the NIRS signal and consequently show an improved performance when trying to modulate it voluntarily during NF training compared with older individuals showing a more rigid NIRS signal change.

Older participants were not able to decrease voluntarily oxy-Hb during one session of NF training. Consequently, young participants showed a superior NF performance when trying to decrease oxy-Hb compared with older ones. The inability of older individuals to decrease oxy-Hb voluntarily during NF training might be related to the observation that older individuals showed an increase in oxy-Hb during the MI offline task while young participants showed a decrease in oxy-Hb. Hence, the natural course of the NIRS signal during MI of swallowing differs between young and older participants. As shown in previous NIRS studies, it is possible to reinforce the natural course of the NIRS signal by means of NF training. In contrast, NF users are not successful in incongruent conditions, in which participants should try to modulate the NIRS signal in the opposite direction than the natural course of the signal (Kober et al., 2015b, 2018). When having a closer look at the oxy-Hb signal change of the older group during NF training (Fig. 3), one can see that older individuals show an initial decrease in oxy-Hb over the right IFG, which is comparable to the oxy-Hb signal change of younger individuals (B1 to B2). Subsequently, oxy-Hb constantly increased from the second to the fourth block. At the end of the training session (B4–B5), oxy-Hb decreased again. Hence, the older group was not able to decrease linearly oxy-Hb over the right IFG. Instead, this group showed some kind of curvilinear response. Oxy-Hb even partly increased during NF training in this group when imagining swallowing movements (B2 to B4), comparable to the oxy-Hb increase during the MI offline task. Hence, older participants of the present study might have been unsuccessful when trying to decrease oxy-Hb during NF training because this is the opposite direction than the natural course of oxy-Hb when imagining swallowing in this older group.

Concerning the subjective ratings of the individual ability to imagine swallowing, we found no statistically significant group differences. However, the descriptive values presented in Table 3 indicate that the older group that was not successful in decreasing oxy-Hb showed lower values than the other groups in the VAS 3 rating, in which they were asked whether they have used a visual or kinesthetic MI strategy. Generally, all participants were instructed to use a kinesthetic MI strategy. Hence, they should imagine how it feels to swallow. Young participants and older individuals who tried to increase deoxy-Hb reported a stronger use of a kinesthetic than visual strategy (values around 70, VAS ranged from 0–100), whereas the older individuals who tried to decrease oxy-Hb indicated to use some kind of mixture of a visual and kinesthetic strategy (value of 56). The used mental strategy might have influenced the NF training performance (Kober et al., 2013). Future studies that directly investigate the mental strategies used during MI of swallowing in NF applications are necessary to address this issue in more detail.

The present study has some limitations. As already mentioned, we did not measure muscle activity during the MI task. Hence, we cannot exclude that older participants produced micromovements during MI, which could not be detected by visual control. In addition, in our statistical analysis, we did not control for a type I error inflation.

The aim of the present study was to show that healthy young and older individuals are generally able to modulate voluntarily the NIRS signal by means of MI of swallowing in a desired direction. How such an NIRS-based NF training can be used in the context of dysphagia rehabilitation and how NF training affects the swallowing function is a matter of future investigations. Especially, the question which feedback parameter should be chosen (either increasing deoxy-Hb or decreasing oxy-Hb) needs further research in the target patient population. Descriptively, in line with prior NIRS studies, deoxy-Hb increased during MI and ME of swallowing in healthy young individuals directly after task onset (Kober et al., 2015a,b, 2018; Kober and Wood, 2014). Deoxy-Hb also increased in the present healthy older group during ME (Fig. 2). Hence, in neurologic patients with dysphagia and in older individuals with no neurologic deficits increasing voluntarily deoxy-Hb during MI of swallowing might lead to a comparable activation of the swallowing motor cortex as during ME. This might increase synaptic plasticity in the swallowing motor cortex and consequently might increase swallowing function (Ros et al., 2014). For oxy-Hb, we found a decrease over the IFG during MI of swallowing in healthy young individuals, whereas oxy-Hb increases during ME (Kober et al., 2015b, 2018; Kober and Wood, 2014). We interpreted this opposite signal change in oxy-Hb between ME and MI of swallowing as a sign of movement inhibition (Kober et al., 2015b, 2018; Kober and Wood, 2014). Hence, when training to decrease oxy-Hb during NF training, this might increase inhibition of the swallowing motor cortex. In the context of dysphagia rehabilitation, it is for instance often reported that neurologic patients with unilateral brain lesions show an overactivation of the affected hemisphere in the chronic phase, whereas healthy individuals with no swallowing deficits show a more bilateral activation pattern (Khedr and Abo-Elfetoh, 2013; Kober et al., 2015a,b, 2018; Kober and Wood, 2014). When the swallowing function improves by natural recovery in patients with dysphagia, the activation patterns of swallowing-related brain areas also become more bilaterally distributed (Ertekin and Aydogdu, 2003). Some prior patient studies could show that external stimulation of the swallowing motor cortex using repetitive transcranial magnetic stimulation (rTMS) leads to recovered swallowing function in patients with dysphagia (Khedr and Abo-Elfetoh, 2013). There is even evidence that an rTMS inhibition protocol (1 Hz) can have positive effects on swallowing function (Khedr and Abo-Elfetoh, 2013; Michou et al., 2016; Verin and Leroi, 2009). In this context, the overactivated, affected hemisphere of patients with dysphagia might not only be inhibited by external stimulation such as rTMS but also by NF training, in which patients learn to decrease oxy-Hb in the affected hemisphere using MI of swallowing. Another approach might be inhibiting the intact hemisphere to decrease transcallosal inhibition by using an oxy-Hb decrease NF protocol. Inhibiting the intact hemisphere by using rTMS was already successfully used to restore the pharyngeal cortex functionality of the affected hemisphere (Cabib et al., 2016; Khedr and Abo-Elfetoh, 2013; Michou et al., 2016). Hence, the effects of the NIRS-based NF training protocols used in the present study to activate/inhibit the swallowing motor cortex on swallowing function need to be evaluated in future studies. Furthermore, it is important to investigate whether NF users are able to modulate the NIRS response in one single hemisphere by means of NF training in future studies.

In summary, our results indicate that there are age-related differences in the within-session trainability of the hemodynamic response, which should be considered when using NF as neurological rehabilitation tool, for instance, to treat dysphagia (Kober et al., 2015a,b; Kober and Wood, 2017a; Szynkiewicz et al., 2018; Yang et al., 2016).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2019.05.022.

Disclosure

The authors declare that they have no competing interests.

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