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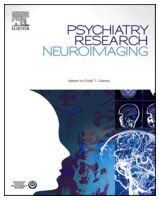

(Interfering) Cortical mechanisms of standing balance and cognition in old-age depression: A functional near-infrared spectroscopy (fNIRS) study

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ABSTRACT

Major depressive disorder in old age can cause changes in the cerebral cortex that might lead to postural imbalance and thus increase fall risk. We aim to examine cortical activation during standing balance in depressed older patients compared to healthy controls and to determine how an additional cognitive task affects this activation. Eleven older patients (age ≥65 years) diagnosed with major depressive disorder and sixteen age-matched healthy controls participated in the study. Functional near-infrared spectroscopy (fNIRS) was used to assess cortical activation of the prefrontal (PFC) and motor (MC) cortex during standing balance with eyes closed under single and dual task (counting backwards). The present study generally revealed tendencies in the MC – and partly the PFC too – for more activation whilst balancing compared to baseline. Also, in the MC, patients tended to show more cortical activation compared to controls and dual task tended to elicit more activation. The results suggest that depressed older patients, to compensate for their illness, may require increased cortical activation to perform motor and cognitive tasks than healthy controls. The absence of PFC activation in the main analyses may be related to the small participant number and possibly to too simple task conditions.

1. Introduction

For the human brain, maintaining standing balance is a complex sensorimotor process involving constant monitoring of balance and counteracting balance disturbances (Fujita et al., 2016; St George et al., 2021; Wang et al., 2016; Kumar et al., 2012). Major cortical areas responsible for maintaining standing balance are the prefrontal cortex (PFC) (St George et al., 2021; Lehmann et al., 2022; Papegaaij et al., 2014; Marusic et al., 2019) and the motor cortex (MC) (Lehmann et al., 2022; Papegaaij et al., 2014), including the supplementary motor area (SMA), premotor cortex (PMC) and primary motor cortex (M1). Impaired functionality in these cortical regions can lead to postural imbalance (Papegaaij et al., 2014). Both, aging (Lehmann et al., 2022; Papegaaij et al., 2014; Rosso et al., 2017) and the presence of major depressive disorder (Pieruccini-Faria et al., 2018) are independently associated with postural imbalance and cerebral alterations. To date, little is known about the extent to which cortical regions controlling standing balance are affected by these influences. A better understanding of cortical alterations in patients suffering from old-age depression is crucial -given that balance deficits might lead to stumbling and even falling (Kumar et al., 2012; Lehmann et al., 2022) - and should facilitate the development of preventive and rehabilitative interventions.

Functional near-infrared spectroscopy (fNIRS) is well-suited to non-invasively – and relatively cost-efficiently - assess activation of cortical brain regions whilst participants perform a standing balance task. In contrast to functional magnetic resonance imaging (fMRI), fNIRS

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measurements can be performed with portable devices and almost no exclusion criteria for participants. Concentration changes of oxygenated (HbO) and deoxygenated/"reduced" (HbR) hemoglobin (Hb) are assessed in the cerebral blood flow. Hemoglobin has different optical characteristics depending on its oxygen concentration. Near-infrared light is emitted and the more HbO is present, the more light is reflected and detected. Activation is given when there is a consistent increase in HbO and a decrease in HbR (Pfurtscheller et al., 2010; Kinder et al., 2022) compared to a control condition.

To date, no fNIRS studies have investigated brain activation in depressed older patients during standing balance. Only a handful of fNIRS studies examined brain activation during standing balance in healthy older persons compared to healthy younger controls – they showed increased activation in the dorsolateral prefrontal cortex (dlPFC) (St George et al., 2021; Lehmann et al., 2022; Marusic et al., 2019; Rosso et al., 2017) and MC (Lehmann et al., 2022) in older persons. With higher difficulty level of standing balance - through manipulation of standing surface/position (St George et al., 2021; Lehmann et al., 2022; Marusic et al., 2019; Rosso et al., 2017), vision, and/or proprioceptive feedback (St George et al., 2021) - activation was again higher in older than in younger participants. These results suggest that maintaining postural control requires higher (probably compensatory) prefrontal activation in older individuals.

Aging (Rosso et al., 2017; Ohsugi et al., 2013) and major depressive disorder (Kumar et al., 2012; Pieruccini-Faria et al., 2018) are both associated with cognitive deficits. Situations in which balance must be maintained whilst cognitive capacity is demanded for an additional task, e.g., standing upright and picking up something from a shelf above the head, might be especially challenging and thus lead to more balance deviations. So far, only a few studies have investigated standing balance combined with an additional cognitive task in healthy older persons; studies in depressed patients are completely lacking. Activation in the (dl)PFC has been shown to increase during simultaneous performance of standing balance and an additional cognitive task in healthy older compared to younger participants (St George et al., 2021; Marusic et al., 2019; Rosso et al., 2017). In this context, the motor cortex has not been studied at all.

So far, there is a lack of research examining brain activation of patients suffering from old-age depression in relation to standing balance. Using fNIRS, this study examines (i) whether there are differences in activation of the PFC and MC during standing balance between older depressed patients and healthy controls and (ii) how performing an additional cognitive task during standing balance affects this activation. Our regions of interest (ROIs) were the PFC (St George et al., 2021; Lehmann et al., 2022; Papegaaij et al., 2014; Marusic et al., 2019) and the MC (Lehmann et al., 2022; Papegaaij et al., 2014), as they have been previously associated with postural control (maintaining standing balance), cognition, and/or dual-task performance. As visual input contributes to balance control (Pieruccini-Faria et al., 2018; Feldman et al., 2020; Lin et al., 2017), we decided to perform the tasks with eyes closed (EC). Without supportive visual input, sensorimotor and attentional resources receive a crucial role in maintaining standing balance. The task becomes more challenging and deficits in these resources might be more evident and easier to identify (Pieruccini-Faria et al., 2018). Counting backwards has been used frequently and successfully as a cognitive task in previous studies on postural control (Papegaaij et al., 2014; Marusic et al., 2019; Swanenburg et al., 2009). According to Swanenburg et al. (Swanenburg et al., 2009) counting aloud was the most appropriate task to interfere with postural control. Based on the literature, we hypothesize that - compared to healthy controls - (i) depressed older patients will show higher activation (more compensation) both in the PFC and MC (SMA, PMC, M1) when comparing "baseline" to "upright standing" as well as (ii) when comparing "upright standing" to "upright standing with additional cognitive task".

2. Material and methods

2.1. Participants

A total of 31 participants took part in this study, of which four patients were excluded from the analyses (1 withdraw consent, 1 aborted the measurement, 2 had data corruption in >10 out of 46 fNIRS channels). Eleven patients (mean age: 71.7 ± 6.8 years; 2 males) and sixteen controls (71.9 ± 4.8 years, 8 males) remained. Psychiatric wards ($N = 1$), practice-based psychiatrists and psychotherapists ($N = 2$) and flyers in public spaces ($N = 8$) were used to recruit older patients who had been diagnosed by their physician with moderate to severe unipolar depression without psychosis. Healthy controls were recruited via flyers in public spaces ($N = 5$), advertisements in online forums for seniors ($N = 7$) and a university course for seniors ($N = 4$). Participants were all able to understand simple instructions and to walk safely ten meters at once. Exclusion criteria included an inability to walk without pain or without a walking aid, comorbidities affecting gait (e.g., orthopedic or neurological disorders), mental disorders relevant to the study (e.g., psychosis, dementia), use of highly potent neuroleptics, severe visual impairment and severe obesity (body mass index/BMI>39). All study procedures were approved by the local ethics committee (EK058/18) and were performed in accordance with the Declaration of Helsinki. The study was registered at Open Science Framework (https://doi.org/10.17605/OSF.IO/A5BJ8). Written informed consent was obtained from all participants before starting the measurements.

2.2. Questionnaires & cognitive assessment

Besides data on demographics and medication, depression and its severity were quantified based on the Geriatric Depression Scale - Short Form (GDS-SF) (Yesavage and Sheikh, 1986) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). Fear of falling was measured using the Falls Efficacy Scale - International (FES-I) (Dias et al., 2006) and mobility using the Timed up and Go Test (TUG) (Podsiadlo and Richardson, 1991). The Mini-Mental-State Examination (MMSE) (Folstein et al., 1975) and two cognitive tests – Trail Making Tests (TMT) A and B (Reitan, 1955) and the Go/No-go test (Zimmermann and Fimm, 2009) – were used to assess cognitive functioning.

2.3. fNIRS data acquisition

Changes in cerebral blood (de)oxygenation were assessed using two mobile NIRSport-1 continuous-wave devices in tandem mode (NIRx Medical Technologies, Berlin, Germany). The optode setup consisted of 16 sources and 16 detectors, resulting in 46 channels with appropriate source-detector distance. Sources/detectors 1–8 belonged to the first, sources/detectors 9–16 belonged to the second NIRS device (see Fig. 1). The sources emitted light with a wavelength of 760 and 850 nm and the detectors sampled the light intensity at 3.47 Hz. The probe setup was designed using the software NIRSite 2021.4 (NIRx Medical Technologies, Berlin, Germany) covering the PFC and MC. The optodes were attached to an electroencephalography (EEG)-cap with appropriate precut slots according to the international EEG 10–5 coordinates. Four different sizes of EEG caps were available for head circumferences of 54, 56, 58 and 58 cm to ensure an optimal cap fit during the measurement. If a participant's head circumference ranged between two cap sizes, the smaller cap size was selected. To prevent the cap from shifting, it was fixed with a strap around the chin. A black plastic overcap was placed on the EEG cap to prevent ambient light from reaching the optodes. The software NIRStar 15.3 (NIRx Medical Technologies, Berlin, Germany) was used for recording. A calibration was performed at the beginning of each measurement to optimize the device settings. Data recording was only started when each channel was marked as "acceptable" or "excellent" by the recording software.

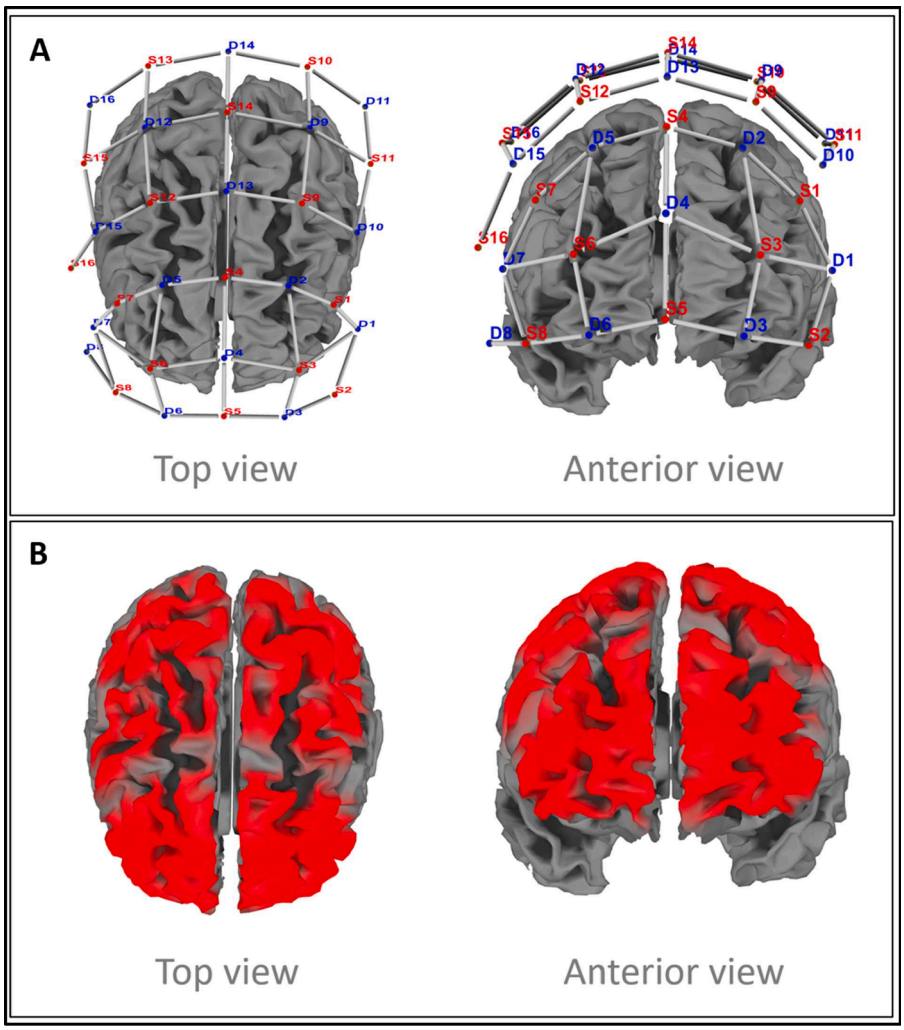

Fig. 1. 3D view of the fNIRS optode montage and fNIRS brain coverage. A *The montage consisted of 16 sources (S; red) and 16 detectors (D; blue), covering the prefrontal and motor cortex.* **B** *The brain regions covered by the optode montage are highlighted in red. Satori 1.8.0 (Brain Innovation B.V., Maastricht, the Netherlands) was used to create this 3D presentation.*

2.4. Experimental tasks

A baseline measurement and two experimental tasks were performed: a single task (ST) and a dual task (DT). Participants were asked to stand with both feet on the ground, eyes closed, wearing socks only, and to avoid any talking or voluntary movements that did not meet the instructed tasks. For the baseline measurement, participants were asked to stand upright and to grasp the back of a chair standing in front of them with both hands. For the experimental tasks, participants were instructed to maintain balance while standing upright with their arms in a relaxed position near the torso, with no additional task (ST) or with simultaneous performance of an additional cognitive task (DT) (see Fig. 2). The cognitive task consisted of counting backwards aloud in ones from a three-digit number randomly chosen by the researcher for each trial. Counting errors were documented by a research assistant (see Table 1).

Each participant completed a total of four runs; two runs were performed for each experimental task (ST and DT, see Fig. 3). The order of runs was chosen randomly for each participant by drawing cards out of an envelope. Each run lasted approximately 140 s and consisted of seven trials – three ST/DT trials and four baseline trials. The design of each run was identical - baseline measurement and experimental tasks alternated at intervals of 20 ± 2 s (jittered interval duration). Each run was initiated and terminated with a baseline trial. During the runs, the German verbal instructions "Loslassen" (English: release) and "Festhalten" (English: grasp) were used to signal the participant to switch between baseline and experimental task. The word "Stopp" (English: stop) signaled the termination of a run. To synchronize the tasks and the fNIRS recording, during the measurement, markers were set manually in the fNIRS recording software for each relevant instruction that was given verbally to the participant ("Loslassen"/"Festhalten" and "Stopp"). Before starting the measurement, participants had time to familiarize themselves with the devices and conditions, and to complete a test run. After each run, participants had a short break to relax (approx. 2–5 min, depending on each participant's request). During this break, it was allowed to open the eyes, move and speak. After finishing the fNIRS measurement, participants filled in a feedback questionnaire concerning task difficulty and burden caused by the fNIRS devices, amongst others.

2.5. fNIRS data preprocessing

fNIRS data preprocessing was performed using Satori 1.8.0 (Brain Innovation B.V., Maastricht, the Netherlands). Raw data trimming was performed for all functional runs, cutting 5 s before the onset of the first experimental condition and 15 s after the offset of the last experimental condition to a total length of 120 s. Raw intensity signals were converted to changes in optical density (OD) calculated from the normalized changes in light intensity incident in the detector from its paired source

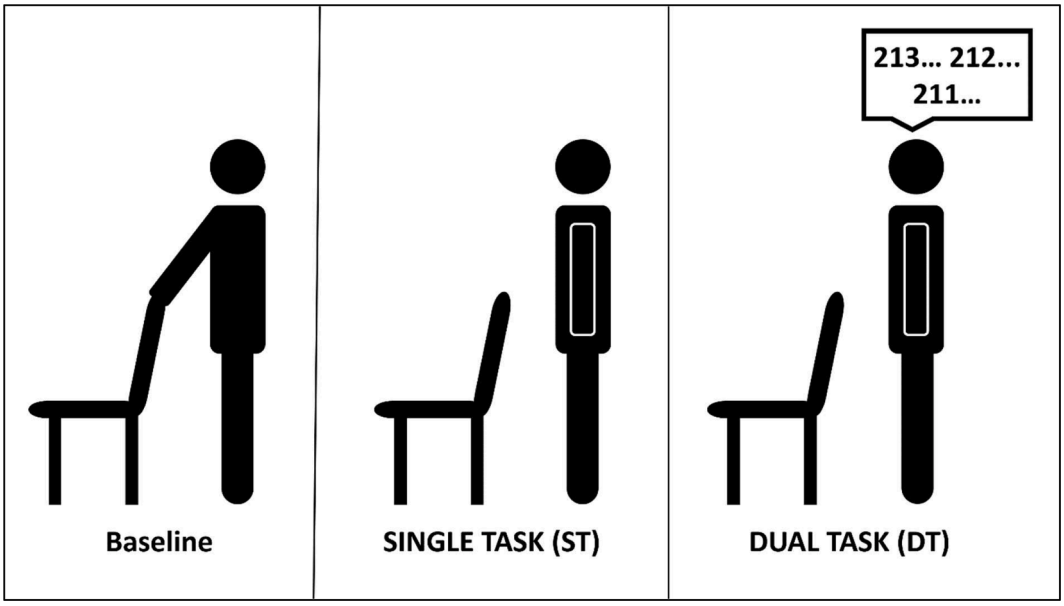

Fig. 2. The baseline measurement and experimental tasks performed during the fNIRS measurement. *Baseline - grasping back of chair with both hands, ST - arms hanging relaxed along the torso, DT - arms hanging relaxed along the torso and counting backwards aloud.*

Table 1
Descriptives of depressed patients (DP) and healthy controls (HC).

Variable	DP ($N = 11$; $f = 9$; $m = 2$) Mean ± SD	HC ($N = 16$; $f = 8$; $m = 8$) Mean ± SD	*p*-value
Age (y)	71.7 ± 6.8	71.9 ± 4.8	0.519
Height (m)	1.58 ± 0.1	1.70 ± 0.1	0.002*
Weight (kg)	66.3 ± 11.0	76.8 ± 11.6	0.027*
BMI (kg/m^2)	26.5 ± 3.5	26.6 ± 3.8	0.941
Depression			
GDS (points)	2.9 ± 2.3	0.7 ± 0.7	0.003*
MADRS (points)	12.5 ± 5.0	2.5 ± 2.4	0.000*
Cognition			
MMSE (points)	28.4 ± 1.4	29.0 ± 0.8	0.284
TMT A (s)	49.0 ± 15.8	37.2 ± 9.4	0.050*
TMT B (s)	90.0 ± 43.7	72.5 ± 28.8	0.264
Go/No-go test (reaction time, ms)	442.8 ± 59.9	439.9 ± 59.2	0.759
Go/No-go test (number of errors)	1.8 ± 2.4	1.1 ± 1.9	0.639
Fear of falling			
FES-I (points)	23.9 ± 6.8	17.8 ± 1.7	0.001*
Mobility			
TUG (s)	9.6 ± 1.6	8.2 ± 2.2	0.208
Dual task performance			
Number of counting errors	0.3 ± 0.6	0.4 ± 0.7	0.684

*f = female, m = male, SD = standard deviation, BMI = body mass index, GDS = Geriatric Depression Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, MMSE = Mini-Mental State Examination, TMT A = Trail Making Test A (connecting numbers in ascending order), TMT B = Trail Making Test B (alternately connecting numbers and letters in ascending order), FES-I = Falls Efficacy Scale – International Version, TUG = Timed Up and Go Test; p-values for normally distributed data (height, weight, BMI, TMT A): unpaired t-tests, p-values for remaining (non-normally distributed) data: Mann-Whitney U tests, * $\alpha < 0.05$.*

position. Motion artifacts were mitigated using the temporal derivative distribution repair (TDDR) motion correction method (Fishburn et al., 2019). Automatic identification and removal of spikes was performed, with variations over 3.5 in OD throughout a time lag of 5 s corrected using a monotonic interpolation. A Butterworth 2nd-order high-pass filter and a Gaussian smoothing-low pass filter, with cut-off frequencies of 0.01 and 0.4 Hz respectively, were applied to remove low-frequency drifts as well as parts of non-hemodynamic related signal components such as heart rate. Additionally, principal component analysis (PCA)-based global component regression was performed to remove other noise components present in all channels. Data were then converted to variations of concentration of oxy- and deoxygenated hemoglobin (HbO and HbR) using the modified Beer-Lambert Law, incorporating a differential path length factor (DPF) of 6.40 and 5.75 for each wavelength, and a z-transform normalization was performed. Channels with missing data were interpolated by averaging the two closest channels.

2.6. Statistical analyses

2.6.1. Description of participant characteristics & behavioral data

Sample characteristics and behavioral data were analyzed using SPSS version 28 (IBM SPSS®, Armonk, NY, USA). Based on the results of the Shapiro-Wilk test, unpaired *t*-tests were applied for normally and Mann–Whitney *U tests* for non-normally distributed data with $\alpha<0.05$ (two-sided).

2.6.2. Neural correlates of standing balance (part 1)

To identify neural correlates of standing balance, a multi-study fixed effects (FFX) general linear model with the contrast "Balance > Baseline" was calculated in Satori for patients and controls, respectively. The threshold applied was $p < 0.05$ (one-sided). Results were visualized as (statistical) t-maps for both, positive values of HbO and negative values of HbR.

2.6.3. Effect of population (patient vs. healthy) and additional cognitive task (single vs. dual) on cortical activation (part 2)

To test whether there was an effect of population and/or additional cognitive task, mixed design repeated measures ANOVAs of β-values were performed separately for HbO and HbR [between-subjects factor: group (patients/controls); within-subjects factor: condition (ST/DT)] using SPSS. All (nine) brain regions activated during standing balance (see part 1 of the analyses) were selected for analysis (ROIs): SMA (Source 9 – Detector 13, S12–D13), left dorsal premotor cortex (dPM) (S9–D9), right dPM (S12–D12), left ventral premotor cortex (vPM) (S11–D10), right vPM (S15–D15, S16–D15), left primary sensorimotor cortex (M1S1) (S10–D9, S11–D9), right M1S1 (S13–D12, S15–D12), left PFC (S1–D1, S1–D2, S2–D1, S2–D3, S3–D1, S3–D2, S3–D3, S3–D4,

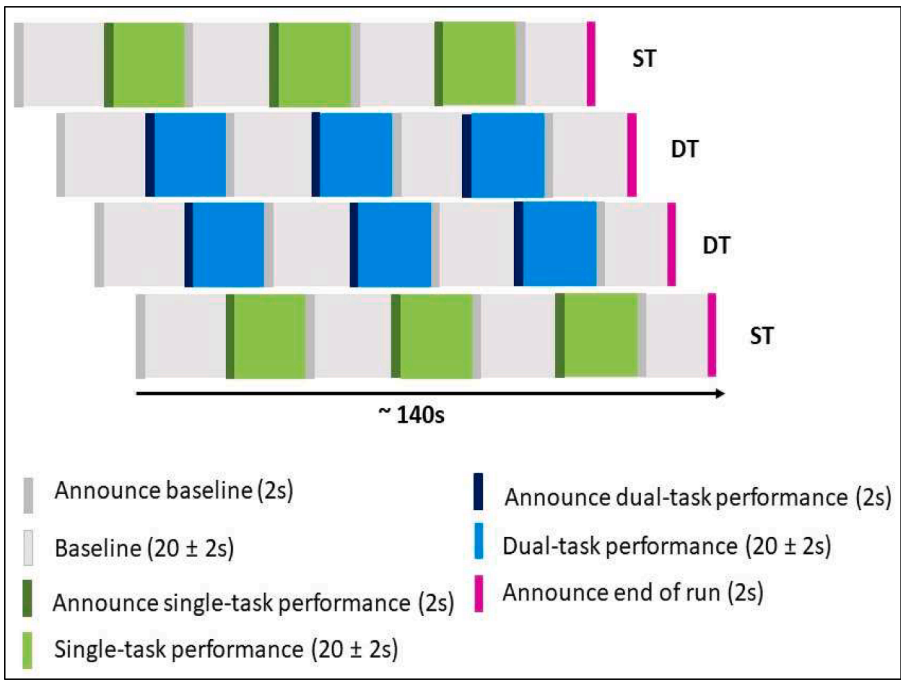

Fig. 3. Exemplary study design. *This figure illustrates an exemplary order of runs for the fNIRS measurement (ST, DT, DT, ST). The order and duration of the different phases of a run (announcement, baseline, experimental task…) are also displayed. ST = single task, DT = dual task.*

S4–D2, S5–D3) and right PFC (S4–D5, S5–D6, S6–D4, S6–D5, S6–D6, S6–D7, S7–D5, S7–D7, S8–D6, S8–D7, S8–D8). The channel selection was based on light intensity maps indicating which channel(s) covered the ROIs best. For the SMA, the right vPM and the M1S1, which were covered by two channels during the measurement, β-values of both channels were averaged before calculating the ANOVAs. For the PFC, channels covering either the left or the right hemisphere were averaged. To correct for multiple testing, we applied Bonferroni correction with $\alpha = 0.05/((9 \times 2)*3) = 0.0009$, with "9″ being the number of ROIs and "2″ reflecting the two conditions. Mean β-values were plotted as graphs to visualize the direction of effects.

3. Results

3.1. Participant characteristics & behavioral data

The descriptives of both participant groups are summarized in Table 1. Patients and controls had a similar age. The patient group consisted mainly of women, while the gender distribution was balanced for the controls – which explains why patients were significantly smaller and lighter than controls (BMI did not differ). On the depression scales, patients consistently scored higher than controls. According to the self-assessment questionnaire GDS, two patients had mild depression and nine had no depression. The external assessment (MADRS) classified one patient as moderately depressed, eight as mildly depressed, and two as not depressed. None of the controls exceeded the cutoff for depression on any of the measures, with one exception on the MADRS questionnaire.

MMSE-based level of cognitive functioning was unrestricted in both groups (all ≥24). Patients tended toward slower performance and more errors on cognitive tests compared to controls. 55 % of the patients rated their fear of falling as moderate, 27 % as low, and 18 % as high. In contrast, 87.5 % of controls reported low and 12.5 % moderate fear of falling. Two patients and one control showed mild mobility impairments (TUG ≥ 10 s). The counting performance during the dual task condition was similar in both groups (9 out of 11 patients without error, controls: 12 out of 16). Patients did not experience the ST condition as easier than the DT condition, whereas controls rated the ST condition as easier than the DT condition (feedback questionnaire, Appendix A). Almost all participants experienced the tasks' difficulty as appropriate rather than too demanding.

3.2. Neural correlates of standing balance

In Fig. 4, the results of the FFX analysis are shown to identify the neural correlates of standing balance. Due to the limited spatial resolution of fNIRS, the labeling of the brain regions should be considered an approximation. It was shown that standing balance induces activation in the SMA, PMC, M1, M1S1 as well as in the primary sensory cortex (S1). Activation of S1 was not considered in the further analyses as we decided a priori to focus on the PFC and the MC. The PFC was activated during standing balance, especially in the frontopolar region. The consistency between HbO and HbR as well as partially between patients and controls was good for both MC and PFC.

3.3. Effect of population and additional cognitive task on cortical activation

As the influence of population and cognitive task on brain activation remained non-significant after Bonferroni correction, detailed information on the ANOVA results can be found in Appendix B but will not be shown/discussed further. Instead, the mean β-values for HbO and HbR are presented in Figs. 5–8 and Appendix C for the nine ROIs to highlight brain-activation tendencies in both participant groups and conditions.

Fig. 5 depicts the mean β-values of SMA. For HbO, it was shown that patients had higher activation of SMA under single compared to dual task. In contrast, controls showed less SMA activation under single compared to dual task. Under dual task conditions, both participant groups showed a similar activation. For HbR, patients exhibited lower activation than controls.

Fig. 6 displays the mean β-values of the dPM. Regarding HbO, the left dPM showed activation for patients only under dual-task condition. The right dPM was activated under both single- and dual-task condition in patients. For controls, no activation was present except in the right dPM

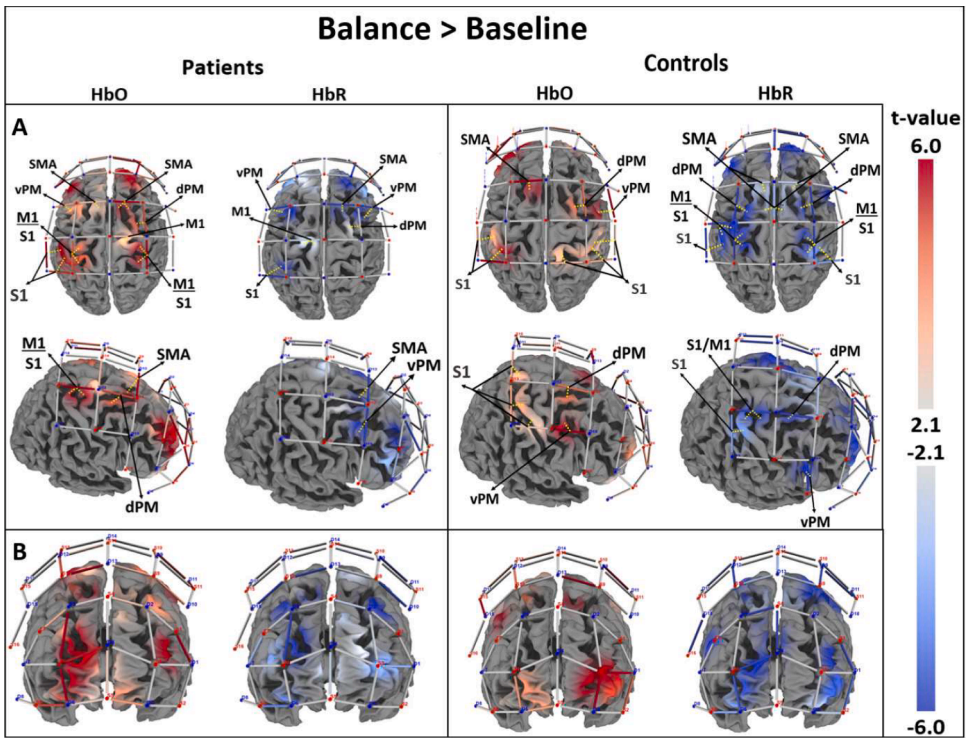

Fig. 4. ***Neural correlates of standing balance (FFX groupwise results; p-value*<0.05 (one-sided)).** *The figure displays cortical activation patterns (t-maps) elicited during maintaining balance in an upright position with eyes closed:* ***A*** *– within motor cortex,* ***B*** *- PFC – overlaid to a 3D cortical surface reconstruction (of individual anatomical data set). The color bar visualizes the range of the t-values. Only positive HbO as well as negative HbR values signal brain activation. HbO = oxygenated hemoglobin, HbR = deoxygenated hemoglobin, SMA = supplementary motor area, dPM = dorsal premotor cortex, vPM = ventral premotor cortex, M1 = primary motor cortex, M1/S1 = primary sensorimotor cortex, S1 = primary sensory cortex.*

under dual task condition. The previously described tendencies are to some extent also true for the HbR values of patients as well as for controls.

Fig. 7 depicts mean β-values of the vPM. HbO and HbR showed a very good consistency (almost mirrored) in both participant groups. Patients showed no activation of left and right vPM under single task condition and only minimal activation under dual task condition in the right vPM. Controls showed activation of the left vPM under dual task condition and (minimal) right vPM activation under single task condition.

Fig. 8 displays the mean β-values of the left and right M1S1. For HbO, patients showed higher activation of left and right M1S1 under single and dual task compared to controls, which showed no activation at all. The consistency between HbO and HbR values was low.

Mean β-values of the PFC were nearly zero for both participant groups under both conditions. Thus, no task specific PFC activation could be ascertained (Appendix C).

4. Discussion

Given the increased postural imbalance and associated fall risk of depressed older patients, an improved knowledge on how a combination of major depressive disorder and aging affects cortical mechanisms related to standing balance is crucial for the development of preventive and rehabilitative interventions (St George et al., 2021; Lehmann et al., 2022; Papegaaij et al., 2014). The present study generally revealed tendencies in the MC – and partly the PFC – for more activation whilst balancing compared to baseline. Also, in the MC, patients tended to show more cortical activation compared to controls and the dual-task condition (standing balance with additional cognitive task) tended to elicit more cortical activation compared to single-task performance (standing balance only).

4.1. Neural correlates of standing balance

Our findings are in line with previous fNIRS studies that found activation in the PFC (St George et al., 2021; Lehmann et al., 2022; Marusic et al., 2019; Rosso et al., 2017) and in the MC (Lehmann et al., 2022) for standing-balance tasks (see Fig. 4). Former studies investigating neural correlates of balancing during motor imagery and/or action observation using fNIRS (Almulla et al., 2022), fMRI (Taube et al., 2014; Mouthon et al., 2018) or positron emission tomography (Malouin et al., 2003) also found activation in the PFC and/or the MC.

4.2. Effect of population and additional cognitive task on cortical activation

When conducting the combined analyses (mixed design repeated measures ANOVAs), the influence of population and cognitive task on brain activation did not remain significant after correction for multiple testing. The number of participants was probably too small to detect effects. Nevertheless, we would like to briefly comment on the tendencies that could be observed (see Figs. 5–8 and Appendix C), as these might still be trendsetting for future studies.

4.2.1. Motor cortex

Compared to healthy controls, patients have to compensate for depression-related (Pieruccini-Faria et al., 2018) – in addition to age-related (Lehmann et al., 2022; Papegaaij et al., 2014; Rosso et al., 2017; Heuninckx et al., 2008; Kubica et al., 2019) – cortical changes. In previous studies, increased cortical activation correlated positively with improved task performance (e.g., complex interlimb coordination task or standing with altered sensory states) in older persons (Heuninckx et al., 2008; Kubica et al., 2019). The tendency toward higher MC activation in depressed older patients may thus reflect compensatory processes. A similar mechanism might apply to the difference between single and dual (more MC activation) tasks.

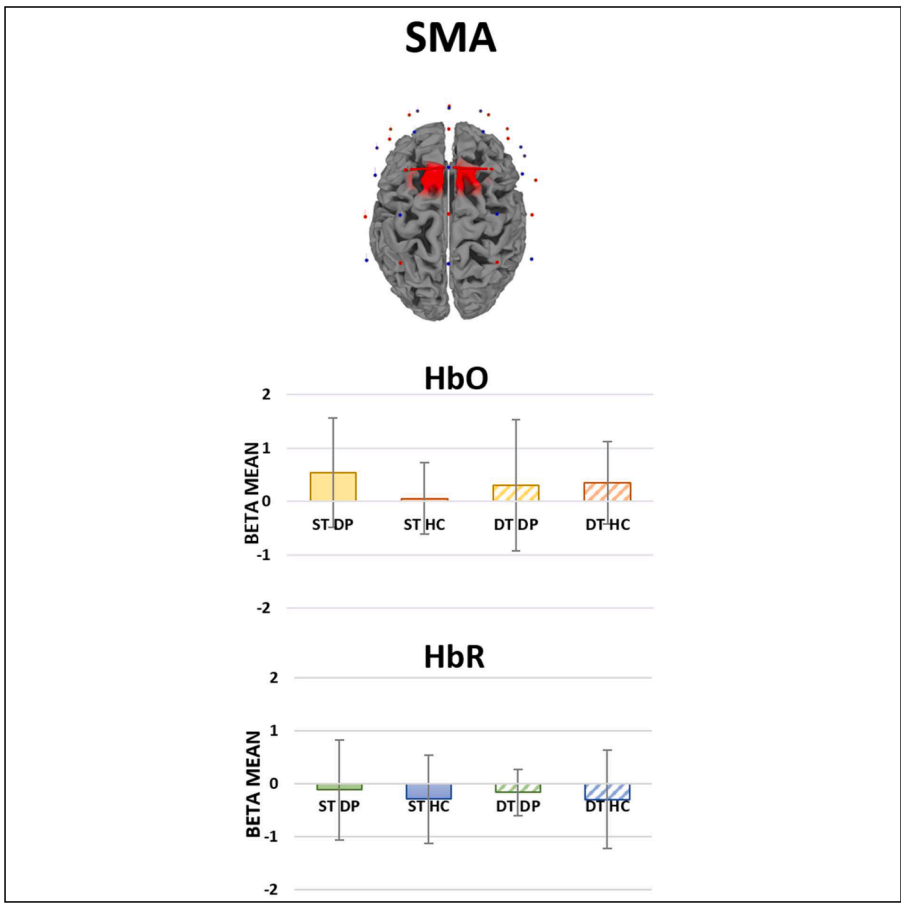

Fig. 5. ***SMA activation under ST and DT for both participant groups.*** *Only positive HbO as well as negative HbR values signal brain activation. The region highlighted in red indicates the brain area defined as SMA. SMA = supplementary motor area, HbO = oxygenated hemoglobin, HbR = deoxygenated hemoglobin, ST = single task, DT = dual task, DP = depressed patients, HC = healthy controls.*

4.2.2. *Prefrontal cortex*

The PFC is believed to be involved in the regulation of balance (Zhuang et al., 2022) as well as cognitive capacities such as executive function or multitasking (coordination of simultaneous and interfering task processing) (Rosso et al., 2017; Zhuang et al., 2022). In addition, the dlPFC is activated during simple arithmetic tasks (Pfurtscheller et al., 2010). Nevertheless, there was hardly any change in activation between single and dual task (see Appendix C). The literature is inconclusive: While Marusic et al. (Marusic et al., 2019) found no difference in PFC activation between single and dual task in either healthy young or healthy older participants, other studies recorded an increase in activation from single to dual task (Fujita et al., 2016; St George et al., 2021) in both.

Under single-task condition, only slight activation was present in the PFC of depressed older patients (see Appendix C). The low PFC activation in depressed patients could be induced by the illness itself, as previous research has found that a symptom such as sadness might be predictive for reduced activation in the frontopolar cortex (part of the PFC) during closed-eye balancing (Helmich et al., 2020) and that affective disorders such as depression are characterized by hypofrontality (decreased blood flow in the PFC) and impaired cognitive and/or executive function (Schecklmann et al., 2011).

The facts that there was only slight activation in the ROIs under the dual-task condition, that both patients and controls were equally able to count backwards almost without errors and their comparable cognitive functioning level (MMSE score) might indicate that the balance and/or cognitive task(s) were not challenging enough. Casteran et al. (2016) also demonstrated that participants suffering from depression and healthy controls were equally able to perform the additional cognitive task in a dual-task condition. However, when the difficulty level to maintain balance was increased, impairments in depressed patients were evident in both postural- and cognitive-task performance (Doumas et al., 2012). As we did not objectively monitor participants' motor performance, no conclusion can be drawn as to whether this was impaired during dual-task performance. Based on our subjective observation, we had the impression that patients tended to sway more than controls. This would be in accordance with previous research on postural performance under dual-task condition of depressed patients, which consistently showed that patients had impaired postural performance (Casteran et al., 2016; Doumas et al., 2012). Future studies should monitor both counting and motor performance in more detail (e.g., counting speed, three-dimensional motion analysis, posturography, video recording) - and both separately and combined - to assess performance and cortical activation on each task individually and which skill is prioritized. The tasks' difficulty could also be increased to potentially elicit a greater effect, as participants reported that the tasks were not too challenging or difficult (see Appendix A).

4.3. *Clinical and cognitive data*

After correction for multiple testing, only non-significant results remained for correlations between HbO values (that, according to our ROI analysis, better reflect activation differences than HbR) and clinical/cognitive data that differed significantly between the groups (GDS, MADRS, TMT-A) (Appendix D). The tendency of patients toward positive correlations between the severity of depression and the activation of MC regions under single or dual task condition supports the assumption that the more severe the depression, the more MC activation is required

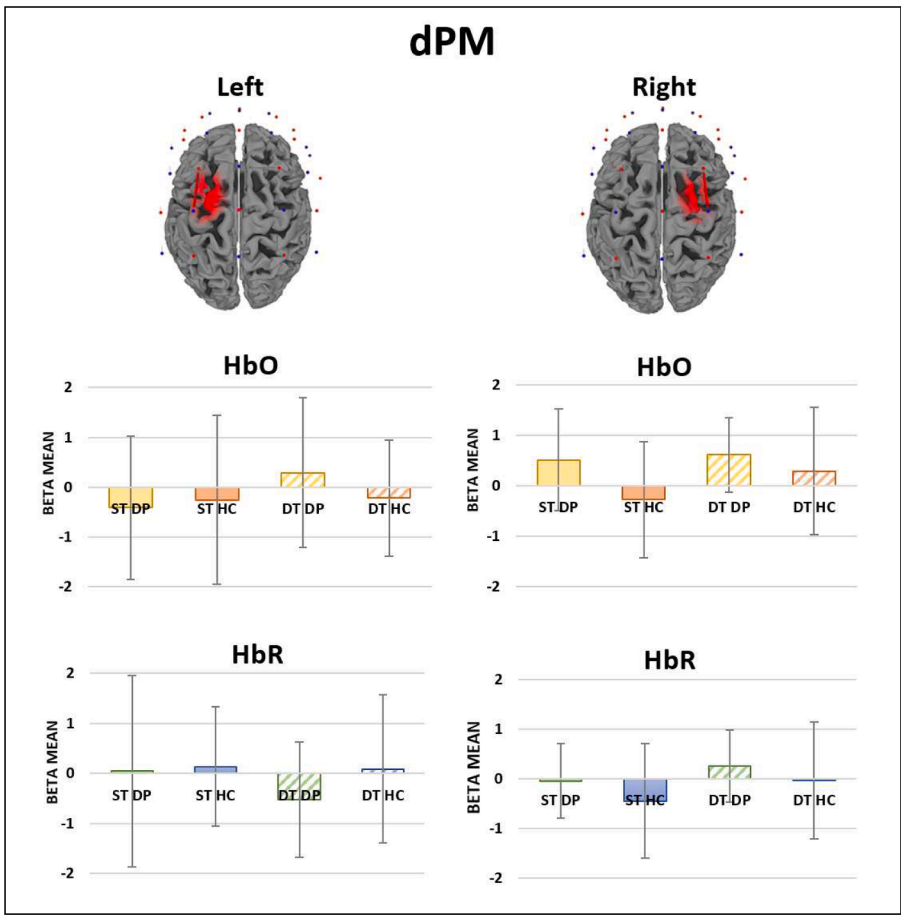

Fig. 6. dPM activation under ST and DT for both participant groups. Only positive HbO as well as negative HbR values signal brain activation. The regions highlighted in red indicate the brain area defined as left and right dPM. dPM= dorsal premotor cortex, HbO= oxygenated hemoglobin, HbR= deoxygenated hemoglobin, ST= single task, DT= dual task, DP= depressed patients, HC= healthy controls.

for task completion. This also agrees with a previous finding showing that activation in the frontal lobe, which is primarily occupied by the MC, positively correlates with depression (Tang et al., 2022). Further, cognitive function level and activation of MC regions under single or dual task tended to correlate negatively. Fewer effects were found for controls compared to patients, which is in line with the assumption that less variance is present in healthy individuals, potentially resulting in lower correlation coefficients. For controls, only the severity of depression and activation of MC regions under single or dual task tended to correlate negatively. The PFC HbO values were not included in the correlation analysis as PFC activation was close to zero.

4.4. Strengths and limitations

Based on the small study population, we cannot draw firm conclusions regarding cortical activation during standing balance and only provide directional tendencies. Nevertheless, this is the first study to examine cortical activation in older patients with major depressive disorder during standing balance under single- and dual-task condition. We provide the proof of principle that measuring cortical activation of depressed older patients using fNIRS is feasible and that robust brain activation for the two conditions could be ascertained with a few trials only. None of the patients reported that the fNIRS measurement was a burden and only one patient suffered from headaches caused by the fNIRS cap during the measurement (see Appendix A). Thus, the generally good data quality and the positive feedback from participants indicate a high potential for the use of fNIRS for future investigations and clinical applications.

A limitation of the study was the suboptimal optode placement, as a part of the cortex that might have been of interest was not covered due to a technical constraint (see uncovered strip of cortex in Fig. 1B). Further, our ROIs could have been better covered by performing a prior MRI for a participant-specific localization of the ROIs and preparation of a participant-specific optode montage, instead of using the EEG standard grid "10–5″. It would probably also be beneficial in future studies to measure more trials in order to collect more data for analysis. A further limitation of the study could be the missing application of short distance channels (SDC). SDC were not standard in the generation of our fNIRS devices (NIRSport-1), but this has changed for devices of the next generation. Signals from SDC – with a smaller distance between source and detector than conventional channels (Yucel et al., 2021) and therewith not measuring brain signals but systemic extracerebral signals – are used to eliminate influences of systemic, extracerebral signals, e.g., heart and respiratory rate or blood pressure, from the fNIRS signal (St George et al., 2021; Yucel et al., 2021; Tachtsidis and Scholkmann, 2016), e.g., by applying a SDC regression method (Wyser et al., 2020). SDCs measure scalp hemodynamics (SDC signals contain mainly systemic and only minimal cerebral activation), which are subtracted from the regular channel hemodynamics (Wyser et al., 2020). Note however, that we used PCA as an alternative to counteract the systemic, extracerebral signals. Another limitation concerns the gender distribution of the patient group; most of the patients were female, which may have influenced the results. It was also striking that some patients did not reach the cut-off value for depression in (some of) the questionnaires, although all patients had a clinical diagnose of major depressive disorder. Possibly the patients were clinically stable, or the depression was already in

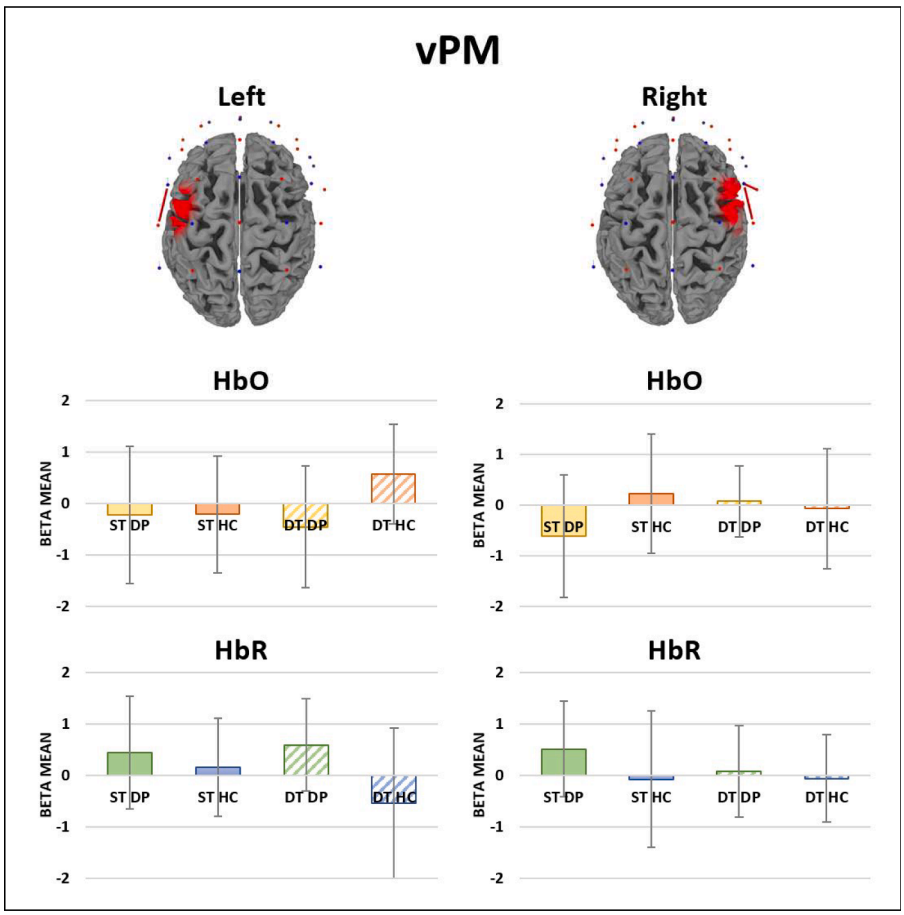

Fig. 7. vPM activation under ST and DT for both participant groups. Only positive HbO as well as negative HbR values signal brain activation. The regions highlighted in red indicate the brain area defined as left and right vPM. vPM= ventral premotor cortex, HbO= oxygenated hemoglobin, HbR= deoxygenated hemoglobin, ST= single task, DT= dual task, DP= depressed patients, HC= healthy controls.

remission.

A strength of this study is that both HbO and HbR values were reported (Kinder et al., 2022; Yucel et al., 2021), since activation is reflected by an increase in HbO and a following slighter decrease in HbR (Pfurtscheller et al., 2010; Kinder et al., 2022). Many previous studies report only HbO, so that it is not possible to track whether activation was actually present or whether non-neural factors (e.g., motion artifacts (Kinder et al., 2022)) were influencing hemodynamic change (positive correlation). Other advantages of reporting both are that statements about data quality (Luke et al., 2021) and consistency are possible. In comparison to many previous studies, this study used a large number of channels for data collection. This allowed the simultaneous examination of multiple cortical regions and to distinguish between regional changes - related to a specific brain region - and global changes - related to the total measured cortical regions (Nieuwhof et al., 2016).

4.5. Suggestions for further studies

Based on our experiences and results, we would like to provide some suggestions for future fNIRS studies in the patient cohort investigated in the current study.

4.5.1. Participant recruitment

- Involve larger participant population to increase statistical power leading to a better generalizability of results.
- Include only participants with severe depression in first instance, most likely effects will be more prominent.

4.5.2. Participant training

- Provide the participants an opportunity to familiarize themselves with the system and run a few test trials before the actual measurement begins.

4.5.3. (Balance) Task selection

- Choose a sufficiently challenging task or increase the difficulty during measurement, simple tasks may not elicit an effect.

4.5.4. Optode setup/placement

- Increase spatial specificity of the fNIRS optode set-up by easy-to-implement possibilities (e.g., use of atlases, fOLD toolbox, probability maps etc.), targeting a more accurate activation measurement of the ROIs.
- Use short distance channels to capture the systemic extracerebral signals from the scalp to be able to remove disrupting signals from the actual signal.

4.5.5. Data collection

- Establish a system to synchronize the trigger setting in the fNIRS acquisition software and the administration of instructions. Possibly use an audio system for providing instructions, which is coupled to the fNIRS acquisition software.

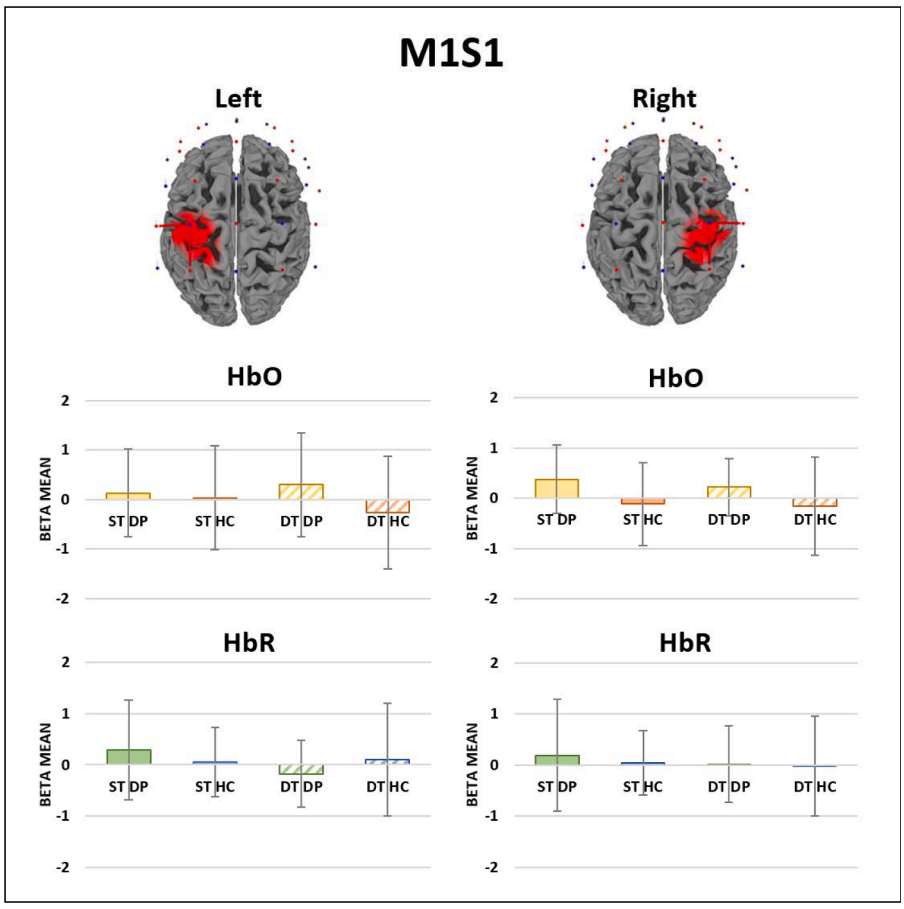

Fig. 8. M1S1 activation tendencies under ST and DT for both participant groups. Only positive HbO as well as negative HbR values signal brain activation. The regions highlighted in red indicate the brain area defined as left and right M1S1. M1S1= primary sensorimotor cortex, HbO= oxygenated hemoglobin, HbR= deoxygenated hemoglobin, ST= single task, DT= dual task, DP= depressed patients, HC= healthy controls.

- Record the body motion as it firstly reflects what influence the conditions have on body motion (e.g., in- or decreased body sway) and secondly, head motion also influences the hemodynamics. For this purpose, during fNIRS measurement, a 3-axial accelerometer could be placed in the head/neck region (at least) or a simultaneous 3D motion analysis could be performed (optimal).
- Record an audio or better a video of the measurement for being able to check the body posture and uninstructed movements as well as the task e.g., counting.

To our knowledge, this is the first fNIRS study to provide information on brain activation in depressed older patients related to "standing balance" (single task) and "standing balance with additional cognitive task" (dual task) compared to healthy older adults. This study demonstrated that fNIRS is feasible to record cortical activation during standing balance in depressed older patients and that sufficient data quality as well as sensible activation patterns (see Fig. 4) can be obtained in this cohort. The findings of our study are partially consistent with our expectations. A replication in larger samples would improve statistical power. A better understanding of underlying mechanisms could help to develop novel preventive and/or rehabilitative interventions to improve standing balance in depressed older persons, especially under dual-task situations, e.g., by neurocognitive and physical training as well as dual-task training which is suggested to provide greatest benefit (Fujita et al., 2016; St George et al., 2021; Lehmann et al., 2022; Ohsugi et al., 2013). The development of appropriate therapeutic interventions should be treated with high priority to counteract the increased risk of stumbling/falling in older depressed patients.

Ethics approval

The study was approved by the local ethics committee (EK058/18) and all procedures were in accordance with the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from all participants.

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CRediT authorship contribution statement

Pia Thönnessen: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **L.Cornelius Bollheimer:** Writing – review & editing, Funding acquisition, Conceptualization. **Michael Luehrs:** Writing – review & editing, Formal analysis, Data curation. **Ute Habel:** Writing – review & editing, Conceptualization. **Bettina Sorger:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Charlotte Huppertz:** Writing – review & editing, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors report no conflicts with any product mentioned or concept discussed in this article.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2024.111905.

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