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Research Paper

Physical and neurobiological depression-associated factors: A cross-sectional study

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ABSTRACT

Background: A diagnosis of depression is traditionally made based on clinical criteria, including current symptomatology and history. This process relies on subjective interpretation only. Identification of objective depression-associated factors using appropriate statistical methods can help formulate prevention and refine treatment programs and policies aimed at reducing depression burden. The purpose of this study was to test whether physical and neurobiological markers might be important depression-associated factors.
Methods: Ninety adults (mean age (SD) 45.7 (10.8) years, 55 females) were categorized as depressed or non-depressed. All were assessed for executive functions, heart rate variability (HRV), gait, and prefrontal cortex oxygenation during walking (measured with functional near-infrared spectroscopy, fNIRS). Least Absolute Shrinkage and Selection Operator (LASSO) regression and planned contrasts were performed to determine independent associations with a diagnosis of depression and assess differences between groups.
Results: LASSO regression analysis resulted in variable selection from gait, executive functions, HRV, and fNIRS measures. The resulting multiparametric model displayed very high predictive power to distinguish non-depressed individuals from those with depression (area under the curve, AUC = 0.946). Planned contrasts revealed that depression significantly differs from non-depression regarding selected single measures of executive functioning (e.g., $r = 0.16$, $p < 0.009$), HRV (e.g., $r = 0.14$, $p = 0.05$), gait (e.g., $r = 0.19$, $p < 0.001$), and fNIRS (e.g., $r = 0.16$, $p = 0.04$).
Conclusions: The identified depression-associated factors can possibly be combinedly used to raise awareness of modifiable factors associated with depression. Our findings warrant further investigations into the causality of the associations to determine their possible utility as modifiable risk factors and to identify their relevance within novel treatments in individuals with depression.

1. Introduction

Depression is a prevalent and disabling disorder associated with a reduced quality of live, somatic comorbidity, psychosocial impairment, premature mortality, and is as disease burden responsible for decreased work productivity (Bromet et al., 2011; Cuijpers et al., 2013; Disease et al., 2018; Kessler, 2012; Lasserre et al., 2016; Mathers and Loncar, 2006). The average (median) true prevalence of psychogenic disorders has been reported to be 9.38 % in the total population ranging from a minimum of 0.3 % to a maximum of 53.5 % (Dohrenwend, 1980), and

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with a lifetime prevalence of 20 % for the general population (Collaborators, 2022). In 2019, about 280 million people lived with depressive disorder, equating to approximately 3.8 % of the world's population (Global Health Data Exchange (GHDx)). Surveys in Switzerland reveal that in the 12 months prior to the survey 5.4 % of respondents had been diagnosed with depression, of which 6.6 % women and 4.2 % men (Schuler et al., 2020). The global prevalence of depression has increased during the COVID-19 pandemic by an estimated 27.6 % (Collaborators, 2021), and the pandemic caused increased adjusted prevalence numbers in Swiss university students with depressive syndrome in 31 % female and 25 % male students (Volken et al., 2021). This substantiates the increased incidence of depression in general observed in the past two decades (Collaborators, 2022).

The way depression is currently diagnosed and the symptom severity described may be reliable, however, is critiqued for lacking validity, e.g., the diagnosis on which two clinicians may come to an agreement does not reflect a disorder connoting an underlying biology (Schatzberg, 2019). Therefore, there are calls to integrate neurobiological markers with clinical characteristics to improve diagnosis (Ho et al., 2022). Currently commonly seen physical symptoms, which also may serve as predictors of treatment response, are not included in *The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for major depressive disorder (Schatzberg, 2019).

Aside from the affective and cognitive problems caused by depression, individuals can present with physical symptoms such as changes in gait (Feldman et al., 2019; Wang et al., 2021; Zhao et al., 2019), changes in heart rate variability (HRV) (Hartmann et al., 2018), and changes in prefrontal cortex oxygenation (Kim et al., 2022). Empirical evidence furthermore suggests that depression is characterized by psychomotor slowing and specific deficits in executive function (Nuño et al., 2021).

First, because gait reflects the integrity of higher brain systems, it can be hypothesized to be a clinically important parameter for psychiatry (Sanders and Gillig, 2010). With an observational gait analysis, clinicians can quickly understand their patients' gait patterns and are able to detect any major abnormalities and, thus, gain important information (Sanders and Gillig, 2010). Visual observation is however not accurate in detecting subtle changes in gait parameters (McGinley et al., 2003). Even though instrumental assessments would be able to confirm the presence and importance of motor abnormalities in depression, there is an identified lack of high-quality studies performing instrumental gait analysis in this population (Belvederi Murri et al., 2020).

Second, HRV parameters have been suggested to be useful as diagnostic or predictive biomarkers of depression as well, however, research is needed to investigate the relationship between HRV parameters and depression (Hartmann et al., 2018; Pizzoli et al., 2021). HRV may for example be used to shed light on pathophysiological processes related to depression such as changes in the central autonomic nervous system (Bassett, 2016), or may be causally linked to depression as shown following HRV biofeedback training (Blase et al., 2021).

Third, prefrontal Cortex (PFC) oxygenation as measured with functional near-infrared spectroscopy (fNIRS), an optical brain monitoring technique, might be a promising parameter as reduced changes in oxyhemoglobin concentrations (HbO_2) have been found in psychiatric patients compared with healthy controls (Yeung and Lin, 2021). For example, interhemispheric asymmetry with lower motor cortical excitability on left when compared to right-side have been observed in depression (Cotovio et al., 2022). Bilateral PFC recruitment when performing simple tasks (instead of mainly right lateral recruitment in healthy persons) and motor cortical resources that are used as compensation during PFC-demanding complex cognitive tasks have also been reported (Tseng et al., 2022). Reasons why fNIRS is suggested as a possible diagnostic biomarker in depression (Nishizawa et al., 2019).

Fourth, evidence derived from systematic reviews shows that deficits in selective attention, working memory, and long-term memory persist in remission from a major depressive episode and these functions worsen with repeated episodes (Nuño et al., 2021; Semkovska et al., 2019). This calls for the need of targeting these cognitive functions in treatment programs, and in programs that aim to prevent relapse (Semkovska et al., 2019).

Summarizing, reduced Heart Rate Variability (HRV) indicates autonomic nervous system dysfunction linked to emotional dysregulation (Sgoifo et al., 2015), slower gait reflects physical slowness and mood (Kan et al., 2025), altered prefrontal cortex oxygenation signals brain hypoactivity in key executive function areas (Uemura et al., 2014), and impaired executive functions—like concentration and planning—demonstrate cognitive deficits caused by frontal lobe dysfunction (Semkovska et al., 2019).

Identification of depression-associated factors using appropriate statistical and diagnostic methods can help to develop new treatments aimed at reducing the depression burden. Development of diagnostic procedures including measurements of gait, cognitive/executive functions, HRV and fNIRS, may help to identify patients with impairments in these domains and establish a basis for targeted therapy interventions to patients' individual mental and physical needs. We hypothesize that parameters of gait, cognitive/executive functions, HRV and fNIRS are associated with depression. The ***primary objective*** of the study is exploring a multiparametric model of depression-associated physical and neurobiological factors to discern depressed from non-depressed individuals. The ***secondary objectives*** encompass assessing whether the most important factors derived from the multiparametric model could individually explain depression symptoms.

2. Materials and methods

2.1. Procedure

The study is a cross-sectional observational study in a hospital setting comparing a group of patients with depression at different severity stages with a non-depressed (self-reported) control group. Assessments with patients were performed at Private Clinic Hohenegg, Meilen and Kantonsspital Winterthur, Winterthur, Switzerland. The non-depressed control group was recruited and measured at Eastern Switzerland University of Applied Sciences OST, St.Gallen, Switzerland.

The assessments were performed every other week on two specific afternoons (Wednesday and Friday) between March and June 2023. Each participant engaged in a single measurement session (Fig. 1) that lasted approximately 50 min. The measurements entailed three distinct phases, with all participants following a standardized sequence as they transitioned between measurement stations. The initial station focused on assessing HRV, followed by the second station, which included two cognitive executive function tests. The final station involved a gait analysis accompanied by fNIRS measurements. Participants arrived in a staggered fashion, and when space permitted, up to three participants were present "simultaneously", although at different measurement stations and in separate rooms.

2.2. Participants

All participants signed a written informed consent. The Ethics Committee of Eastern Switzerland (Ethikkommission Ostschweiz (EKOS)) approved this study (Project-ID 2022–02,261, EKOS 22/204). Data are reported in line with the STROBE Statement (von Elm et al., 2007).

2.3. Inclusion and exclusion criteria for patients with depression

Inclusion criteria were: (a) signed written informed consent, (b) age older than 18 years, and (c) ability to walk two times 3–5 min at individual preferred walking speed (overground walking on flat surface), BDI $\geq$ 10. Exclusion criteria consisted of: (a) unstable cardiovascular condition, (b) history of alcohol or drug abuse, and (c) any current mental or neurological disorder.

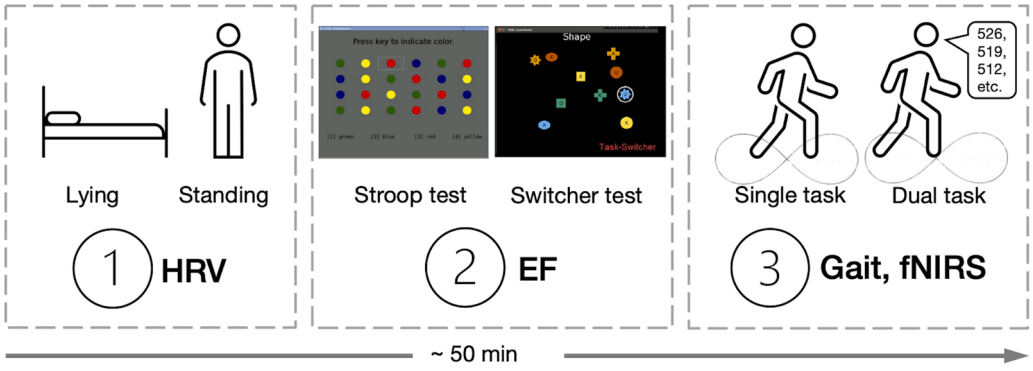

Fig. 1. Procedure of the measurement session with three phases; HRV, heart rate variability; EF, executive functions; fNIRS, functional near-infrared spectroscopy for measuring prefrontal cortex oxygenation during walking.

2.4. Power analysis

A priori power analysis was conducted using G*Power software version 3.1.9.7 (Faul et al., 2007). To attain an 80 % level of statistical power for a three-group cross-sectional comparison design, a sample size of 84 participants would be required. The significance level (α) was set at 0.05, and the effect size *f* was specified as 0.35, a value previously reported in studies comparing healthy individuals with those experiencing depression (Radovanovic et al., 2014).

2.5. Assessment of health and depression

Depression was assessed with the Beck Depression Inventory – Second Edition (BDI-II; (Beck et al., 1996)). The BDI-II is a reliable and valid instrument in both clinical and nonclinical (Canals et al., 2001) populations. It consists of 21 questions, each offering four response options. Each item is evaluated on a scale ranging from 0 to 3, with a total score ranging from 3 to 63. Higher scores reflect a higher severity of depressive symptoms. The BDI-II scores were initially used to dichotomize participants into two groups: a non-depressed control group (absent depression) and a group with mild to severe depressive symptoms. For the ensuing planned contrasts analysis, the group with mild to severe depressive symptoms was classified into two groups: mild depression and moderate-to-severe depression. Based on guidelines for BDI cut-off scores (Beck et al., 1988), the BDI-II scores were defined as: 0–9 as absent or minimal depression, 10–18 as mild depression, and ≥19 as moderate to severe depression. Beck et al. (1988) have pointed out that the cut-off values for the BDI can vary depending on the specific purpose for which the values are used. In our case, we chose the originally reported thresholds from Beck et al. (1988) (Beck et al., 1988) to minimize the likelihood of false positive results, thus opting for a more conservative approach with a lower cut-off point.

The health questionnaire served the purpose of assessing participant's eligibility for the study and documenting any factors that could potentially influence the measurements, including the general health status, pain, and disability.

2.6. Heart rate variability (HRV)

HRV was measured during 7 min in a supine position and subsequently for 3 min in a standing position (Fig. 1). RR-intervals (the time period between consecutive R waves on an electrocardiogram (ECG)) were recorded using a single-lead ECG chest strap and wristwatch (Polar H10 and Vantage M2, Polar Electro Oy, Kempele, Finnland) and was analyzed using Kubios Scientific HRV software (Version 4.0.3, Kubios Oy, Kuopio, Finland). Settings: automatic noise detection = none, beat correction = threshold (custom) 0.2; Very Low Frequency (VLF) range = 0 – 0.04 Hz, Low Frequency (LF) range = 0.04 – 0.15 Hz, High Frequency (HF) range = 0.15 – 0.4 Hz, window width = 60 s, window overlap = 50 %, lomb smoothing = 0.02 Hz, Autoregressive (AR) model order = 16 (Eggenberger et al., 2020).

As HRV is correlated with heart rate, all values were normalized to the latter (Sacha, 2013). Mean heart rate, low frequency (LF, ms^2) power, high frequency (HF, ms^2) power, LF/HF ratio (%), mean beat-to-beat (RR, ms) interval, standard deviation of normal RR intervals (SDNN, ms), root mean square of successive RR intervals (RMSSD, ms), as well as short half axis (SD1, ms) and long half axis (SD2, ms) of fitted ellipse were calculated for the last 3 min of the lying measurement and the 3-minute standing measurement. The data of two participants were excluded from the analyses due to measurement error.

2.7. Executive functions assessment

To assess cognitive abilities, participants completed two minimally modified EF tests from the Psychology Experiment Building Language (PEBL) test library in German (Mueller and Piper, 2014, Anon). First, working memory and inhibition was evaluated with the Victoria Stroop Test. This test entailed three tasks: (i) naming colored dots; (ii) naming the ink color of incongruently printed color words, and (iii) inhibiting the automatic reading response to identify the color of incongruent color words. Throughout the Victoria Stroop Test, the time interval between the first response and the completion of that phase (referred to as *trialtime*), and the number of errors (referred to as *incorrect*) were recorded.

Subsequently, cognitive flexibility or task switching was assessed with the Switcher Task. In this test, participants were presented with a series of trials, each involving a specific task or set of rules (e.g., letter and shape), and were required to switch between them as instructed. The test aims to evaluate response times and the impact of task-switching on performance. The duration between the initial participant response and the finish of the specific phase (referred to as *perftime*), and the score of errors made by the participants (referred to as *numerr*) were recorded.

2.8. Gait assessment

Gait characteristics were measured by two inertial sensors (Physilog 6, GaitUp SA, Lausanne, Switzerland) fixated on the shoes. Data were analyzed with Gait Analyser software (Gait Up, Lausanne, Switzerland) using standard settings. Gait data was filtered by excluding single data points 20 % larger or smaller than the median. The following features were extracted and reported as the combined mean of the left and right foot: gait speed, gait cycle time variability, step length variability, minimal toe clearance, step width, 3D path length, and symmetry, as well as stance, swing, and foot flat time. If there were <30 recorded gait cycles (i.e., 60 steps) due to measurement error, the dataset was excluded from the analysis and only data of the other foot was used. This

cut-off is well above the minimum required steps to acquire excellent reliability when analyzing gait variables using an acceleration sensor (Menz et al., 2003).

Gait was assessed during over ground walking performed on a figure-of-eight gait path, and the participants were wearing their own shoes for walking (Fig. 2). The duration of each trial consisted of 10 complete loops at self-selected, preferred walking speed, which is usually (based on previous testing in our lab) equivalent to a duration of around 3–5 min. Participants performed two trials, with the first trial including the single-task (ST) condition, i.e., walking without an additional cognitive task. The second trial includes the dual-task (DT) condition, where participants were asked to count backwards in steps of 7 from a random number between 500 and 550.

2.9. Functional near-infrared spectroscopy (fNIRS)

Brain activity of the PFC was assessed during gait analysis, using a standardized approach (Menant et al., 2020) and two tissue oximeters (OXYPREM 1.4, OxyPrem AG, Zurich, Switzerland). The two sensors were positioned next to each other on the participant's forehead over the areas between Fp1-F3-F7 and Fp2-F4-F8, respectively, related to the international 10/20 electrode placement system (Eggenberger et al., 2016; Leff et al., 2008). They were fixated on the skin with a skin friendly tape (Fixomull stretch, BSN medical, Hamburg, Germany) and a self-adhesive bandage (Dermaplast CoFix, Neuhausen, Switzerland). To decrease light irradiation, an elastic bandage was affixed on top of the self-adhesive bandage. The sensors were then connected to a tablet. They were synchronized and simultaneously the manual stopwatch was started. The stopwatch was required to determine rest and walking phases throughout the gait assessment. The tablets were then stored in a backpack worn by the participant. Data were collected at a sampling rate of 1 Hz. The mean of both left and right oxygenated hemoglobin (O_2Hb) during single- and dual-task walking was measured and used for further analyses. Processing of fNIRS data was performed through internal software algorithms of the OXYPREM tissue oximeters.

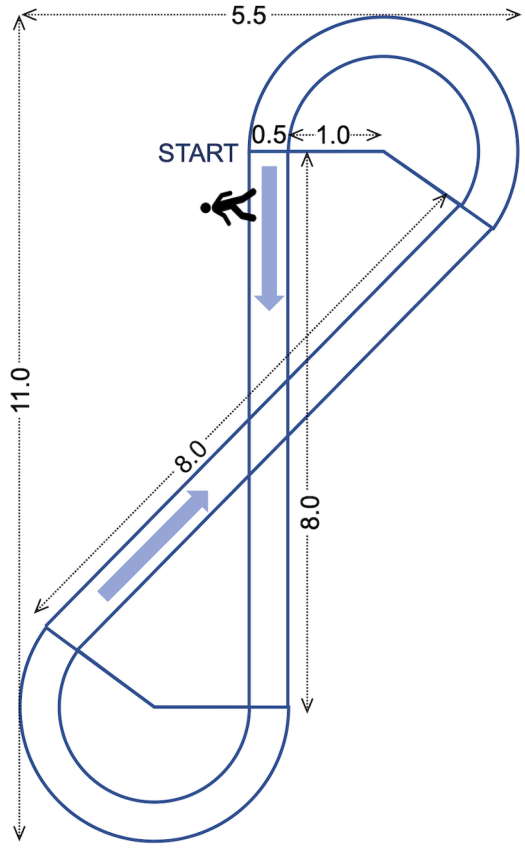

Fig. 2. Figure-of-eight gait path.

2.10. Statistical analyses

Normality of the data was tested with the Kolmogorov-Smirnov test. Descriptive statistics were used to define the study population and to calculate gait characteristics.

Related to our primary objective, a Least Absolute Shrinkage and Selection Operator (LASSO) regression model was used to establish a prediction model for depression and identify the most important predictive parameters (Fig. 3). We used a BDI-II-based dichotomous classification (healthy control vs. depression) of the participants as dependent variable and used the described depression-associated factors as independent variables, including the parameters from HRV, Executive Function, gait, and fNIRS measurements during walking. The importance of each parameter in the prediction model was evaluated based on its standardized beta-coefficient. Receiver Operating Characteristics (ROC) analysis was used to analyze the capability of the test battery values in distinguishing between the healthy control group (absent or minimal depression) and participants with mild to severe depression, and to characterize prediction model accuracy (Obuchowski and Bullen, 2018) through sensitivity and specificity and performance through area under the ROC-curve (AUC).

In accordance with our secondary objective, we used planned contrast analyses to evaluate if the ten most important parameters derived from the LASSO model could independently discriminate three groups of participants, i.e., "*healthy control*", "*mild depression*" and "*moderate-to-severe depression*" (Field, 2009). For the set of contrasts, we compared the two experimental depression groups (mild depression and moderate-to-severe depression) to the healthy control group as contrast 1, and then compared the mild depression group to the moderate-to-severe depression group in the second contrast (Field, 2009).

Missing values due to measurement error were not imputed. In addition, we did not apply a correction for multiple testing (such as the Bonferroni or Holm method) for the following reasons. First, we applied LASSO regression to establish the primary multiparametric model, which encompasses variable selection and reduction, and thus inherently minimizes issues with multiple comparisons and model overfitting. Second, in our secondary analysis using planned contrasts, only the ten most important variables were selected based on the LASSO results. Third, since our study is exploratory in nature it was recommended that corrections for multiple comparisons should not be applied for this type of studies as they may increase Type II errors and hinder the generation of novel hypotheses for future research (Perneger, 1998; Streiner and Norman, 2011). Therefore, we prioritized the evaluation of effect sizes and basic logical considerations for the interpretation of the statistical results (Cabin and Mitchell, 2000; Moran, 2003).

Statistical calculations were performed with RStudio, version 4.1.3 (R Core Team, 2022) and R Markdown (Xie et al., 2019) statistic software. The significance level was set at $\alpha = 0.05$. Definition of the effect size r followed Cohen's (1988) criteria, where a small effect size is at $r = 0.10$, a medium effect size at $r = 0.30$, and $r \geq 0.50$ is considered as a large effect size (Gignac and Szodorai, 2016).

3. Results

Data from 90 individuals were included for analysis and interpretation, i.e. 36 non-depressed controls and 54 individuals with depression. Demographic and clinical characteristics of all individuals are illustrated in Table 1. Sixty-eight participants performed the fNIRS measurements, which was not mandatory for participating in the study (i.e., 72 % of the total sample).

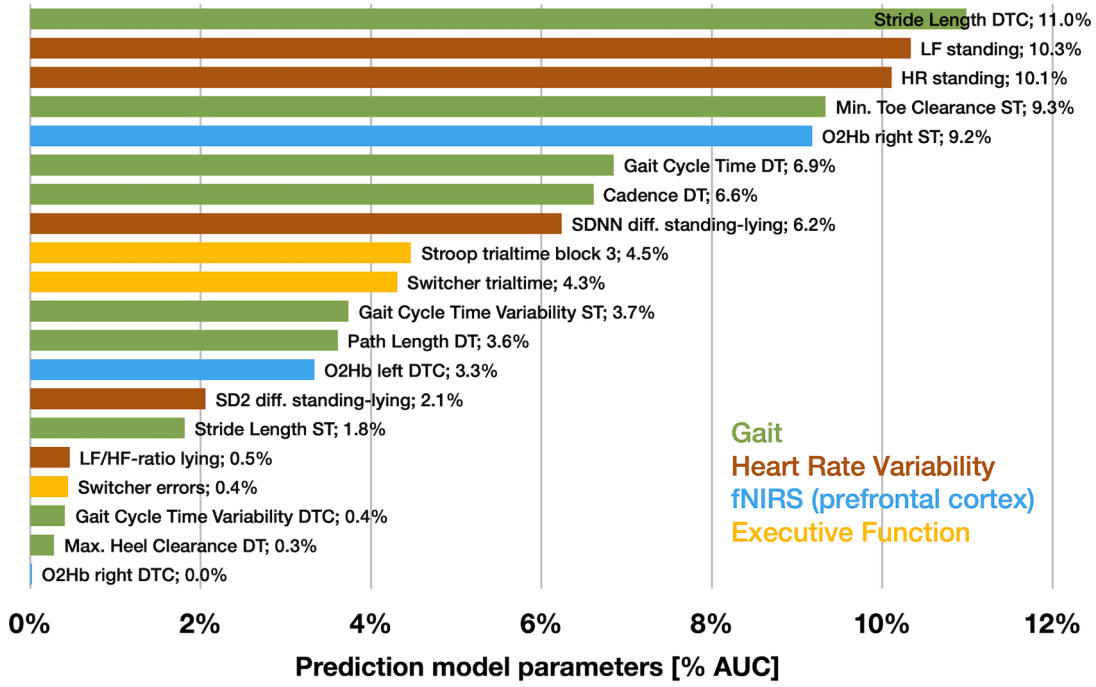

Fig. 3. Depression-associated factors of the LASSO regression model for differentiating the healthy control from the depression group
Legend: AUC, area under the curve; BDI-II, beck depression inventory – second edition; DT, dual task; HF, high frequency; LASSO, least absolute shrinkage and selection operator; LF, low frequency; ST, single task; RMSS, root mean square of successive R–R interval differences;SDNN, standard deviation of the NN Interval.

Table 1
Demographic and clinical characteristics of each group.

Variable	Non-Depressed Control Group (BDI-II: 0–9)	Depression (all) (BDI-II: ≥10)	Mild Depression (BDI-II: 10–18)	Moderate-to-Severe Depression (BDI-II: ≥19)
N (EF, HRV, gait)	36	54	19	35
N (additionally fNIRS)	26	42	16	26
Sex, female (%)	22 (61.1 %)	33 (61.1 %)	10 (52.6 %)	23 (65.7 %)
Age, years	45.3 ± 10.8	46.1 ± 11.0	47.1 ± 11.4	45.5 ± 10.8
Height, cm	171.6 ± 8.6	169.7 ± 9.2	170.9 ± 9.0	169.1 ± 9.4
Weight, kg	74.2 ± 12.6	78.0 ± 19.4	83.1 ± 16.0	75.3 ± 20.8
Education, years	14.0 ± 1.4	13.0 ± 2.0	13.6 ± 1.5	12.7 ± 2.2
BDI-II score	4.4 ± 3.0	23.4 ± 10.0	13.6 ± 2.6	28.7 ± 8.4

Data are numbers or means, BDI-II, Beck Depression Inventory – Second Edition; EF, executive functions; fNIRS, functional near-infrared spectroscopy; HRV, heart rate variability; DTC, dual task cost; N, number of participants. Measures of variability is Standard Deviation.

3.1. Multiparametric prediction model based on EF, HRV, gait, and fNIRS measurements

The LASSO regression analysis for predicting depression (“*healthy control*” vs. “*depression*”) resulted in parameter selection from all four measurement domains of factors associated with depression: gait, executive functions, HRV and fNIRS (Fig. 4). The multiparametric prediction model resulted in an area under the curve (AUC) of 0.946, indicating strong model performance for discriminating between healthy control (absent or minimal depression) and depression (BDI-II score ≥ 10). The receiver operating characteristic curve (ROC curve) from the prediction model had a sensitivity of 93 %, and a specificity of 88 %.

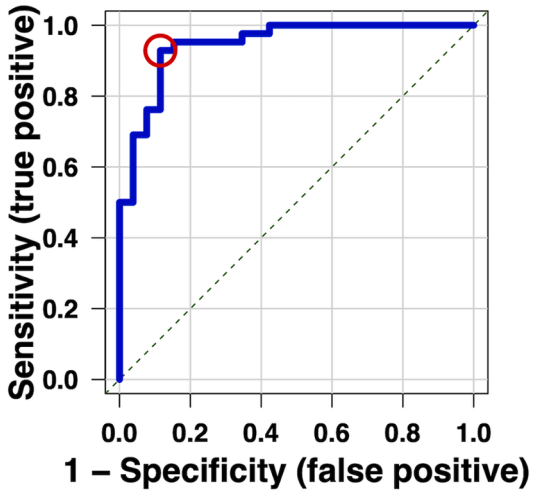

Fig. 4. ROC curve of the LASSO regression model for differentiating “healthy” from “depression”.

3.2. Planned contrasts of EF, HRV, gait, and fNIRS parameters

We selectively calculated planned contrasts for the ten parameters with the highest contribution to the LASSO prediction model (Fig. 3). Results of the planned contrasts 1 and 2, respectively, are shown in Tables 2 and 3. Exemplary results from significant contrast 1 analyses are depicted in supplementary figures 1 and 2AB.

4. Discussion

4.1. General findings

The aim of this study was to identify and quantify important factors associated with depression using physical and neurobiological markers

Table 2
Results of planned contrast 1 for the ten most important parameters derived from the LASSO model ("non-depressed controls" vs. "depression").

Measurement	Parameter	Non-depressed		Depression		Contrast 1			
		mean	SD	mean	SD	df	t	p (one-tailed)	r
Gait	Stride Length DTC [%]	−4.49	4.80	−4.28	4.94	88	−0.019	0.492	0.01
	Gait Cycle Time DT [s]	1.08	0.09	1.15	0.12	88	2.975	0.002**	0.18
	Min. Toe Clearance ST [m]	0.023	0.009	0.022	0.008	88	−0.452	0.326	0.07
	Cadence DT [steps/min]	112.1	9.9	105.3	11.0	88	−3.006	0.002**	0.18
HRV	HR standing [beats/min]	83.5	12.8	88.8	13.4	88	1.654	0.051	0.14
	LF standing [1/ms]	0.00219	0.00192	0.00153	0.00219	88	−1.145	0.128	0.11
	SDNN diff. standing-lying [%]	77.86	60.59	90.51	69.61	88	1.592	0.058	0.13
EF	Switcher trialtime [s]	234.79	53.11	263.18	64.90	88	2.033	0.023*	0.15
	Stroop trialtime block 3 [s]	19.81	7.62	25.39	12.26	88	2.428	0.009**	0.16
fNIRS									
	O_2Hb right ST [μM]	47.53	15.68	54.31	15.59	66	1.749	0.042*	0.16

Bold values indicate significance, *p < 0.05, **p < 0.01, ***p < 0.001; DT, dual task; EF, executive functions; fNIRS, functional near-infrared spectroscopy; HRV, heart rate variability; left, left hemisphere; LF, low frequency; O_2Hb, oxygenated hemoglobin; right, right hemisphere; SD, standard deviation; SDNN, Standard Deviation of the NN Interval; ST, single task.

Table 3
Results of planned contrast 2 for the ten most important parameters derived from the LASSO model (mild depression vs. "moderate-to-severe depression").

Measurement	Parameter	Mild depression		Moderate to severe depression		Contrast 2			
		mean	SD	mean	SD	df	t	p (one-tailed)	r
Gait	Stride Length DTC [%]	−5.31	4.06	−3.72	5.33	52	1.144	0.128	0.15
	Gait Cycle Time DT [s]	1.16	0.14	1.14	0.11	52	−0.473	0.319	0.09
	Min. Toe Clearance ST [m]	0.022	0.009	0.022	0.008	52	−0.216	0.415	0.06
	Cadence DT [steps/min]	104.4	13.3	105.8	9.7	52	0.456	0.325	0.09
HRV	HR standing [beats/min]	86.5	11.3	90.0	14.4	52	0.930	0.178	0.13
	LF standing [1/ms]	0.00215	0.00278	0.00119	0.00175	52	−1.636	0.053	0.17
	SDNN diff. standing-lying [%]	130.4	67.3	68.8	61.5	52	−3.464	< 0.001***	0.25
EF	Switcher trialtime [s]	257.45	66.24	266.30	64.91	52	0.511	0.305	0.10
	Stroop trialtime block 3 [s]	25.93	13.02	25.10	12.01	52	−0.271	0.393	0.07
fNIRS									
	O_2Hb right ST [μM]	55.16	14.87	53.79	16.28	40	−0.273	0.393	0.08

Bold values indicate significance, ***p < 0.001; DT, dual task; EF, executive functions; fNIRS, functional near-infrared spectroscopy; HRV, heart rate variability; left, left hemisphere; LF, low frequency; O_2Hb, oxygenated hemoglobin; right, right hemisphere; SD, standard deviation; SDNN, Standard Deviation of the NN Interval; ST, single task.

and clinical characteristics. From four potential depression-associated measurements (i.e., gait, executive functions, HRV, and fNIRS), the LASSO regression model included parameters from all four measurement domains. This resulted in the explanation of a large portion of depression. Both the sensitivity and the specificity of the analysis resulted in high values and indicated the test's ability to correctly classify a person as having depression or not having depression. Our current findings imply that a clinical diagnosis of depression based on the reported current symptomatology and history may become more valid when extended with physical and neurobiological markers. More in detail, a clinical diagnosis based on the reported current symptomatology and history could be enhanced via the assessment of gait, executive functions, HRV, and fNIRS. The high sensitivity observed means that there were only a few false negative classifications, and thus, when this assessment is applied in clinical settings, we can expect that fewer cases of depression will be missed. Furthermore, the high specificity of our assessment means that there were few false positive results. However, our current model, including parameters from gait, executive functions, HRV, and fNIRS, serves as an exploratory framework. Future research, particularly longitudinal and validation studies, will be necessary to identify a parsimonious subset of factors that retain diagnostic accuracy while ensuring clinical feasibility.

Our study does confirm our hypothesis. First, the current findings confirm that gait parameters could be a potentially important clinical marker for diagnosing depression. Gait variability and cognitive function have previously been shown to share neural substrates (Byun et al., 2023), and high gait variability is a marker of cognitive-cortical dysfunction hypothesized as being helpful with the identification of Alzheimer's disease dementia (Pieruccini-Faria et al., 2021). The gait changes that we observed in dual task walking relative to single task

walking are consistent with these studies and demonstrate that also in people with depression cognitive tasks have a destabilizing effect on gait (Grabiner et al., 2001; Hollman et al., 2007; Menz et al., 2003; van Iersel and al., 2007; Woollacott and Shumway-Cook, 2002). This is in line with observations that executive dysfunction in people with depression effects on their gait (Wright et al., 2011). Importantly, the dual tasking paradigm is also useful for the differential diagnosis of depression and mild cognitive impairment since those with cognitive mild impairment show higher dual task costs than those with depression (Metzger et al., 2016). This seems to indicate that it is clinically relevant to consider additional cognitive tasks in gait assessment of people with depression. So far however, little or no attention was paid to cognitive disorders associated with depression (Perini et al., 2019). Previous research demonstrated that cognitive alterations are a core clinical feature of depression and should, therefore, not be considered merely secondary to it (Miskowiak et al., 2016; Perini et al., 2019). When cognitive problems are among the main causes of functional impairment in those with depression, they should be regarded as a partially independent dimension of depression, and consequently an important target of treatment (Miskowiak et al., 2016). Future research should assess whether such treatments may be non-pharmacological in nature, similar as seen in older adults with depression (Apóstolo et al., 2015; Drazich et al., 2020; Fernandes et al., 2022; Yen and Chiu, 2021).

Second, the current findings also confirm our hypothesis that executive parameters could be a potentially important clinical marker for diagnosing depression. It has been demonstrated already previously that people with depression show impairments across a wide range of executive functions, and this may negatively impact their everyday functioning (Stordal et al., 2004). Executive function is also considered an important link between depression and cognition and studies observed the direct relation between executive function, gait speed and dual task costs (Coppin et al., 2006; Yogev-Seligmann et al., 2008). In our study, non-depressed controls differed from individuals with depression. Past research demonstrated that fatigue/energy was the most important underlying reason for the observed poor executive functioning in those with depression (Kraft et al., 2023). In case this relation is confirmed to be causal, it will offer a rationale for innovative forms of physical training such as video game play in a standing position as this might have an effect on executive functioning (Stanmore et al., 2017). Future studies seem warranted that assess this relationship.

Third, the present study investigated the association between HRV measurements and depression and confirmed our hypothesis that certain HRV parameters exhibit a substantial potential for differentiation between non-depressed and depressed individuals. The ability to discriminate between varying degrees of symptom severity was however less pronounced. Specifically, SDNN (lying) and HF (lying) demonstrated significant differences with small to medium effect sizes when comparing non-depressed to depressed individuals. These observations match previous results where lower HRV-measures in people with depression were interpreted as a cardiovascular risk factor (Koch et al., 2019) or estimated as being reflective of decreased cardiac vagal tone and elevated sympathetic activity (Servant et al., 2009).

Considering the separate outputs from the HRV measurement device, we observed that SDNN (% difference standing-lying), RMSSD (lying), RMSSD (% difference standing-lying), and HF (% difference standing-lying) were significantly associated with distinguishing between our experimental groups. Notably, SDNN (% difference standing-lying) and RMSSD (% difference standing-lying) exhibited medium effect sizes, indicating their potential as reliable markers for separating between mild and moderate-to-severe depressive symptoms. RMSSD (lying) displayed a smaller effect size in this context, while HF (% difference standing-lying) demonstrated almost a medium effect size. In summary, while some parameters, like SDNN (lying) and HF (lying) are more indicative of the presence of depressive symptoms, others, such as SDNN (% difference standing-lying), RMSSD (lying), RMSSD (% difference standing-lying), and HF (% difference standing-lying), are better suited for assessing the severity of these symptoms. Meanwhile, LF/HF ratios do not appear to be strongly associated with BDI-II scores. These findings underscore the need to carefully select HRV parameters based on the specific clinical objectives related to depression assessment.

Finally, contrary to our initial hypothesis, differential responses in brain activity during ST and DT walking, showed no support for the idea that PFC activity is lower in patients with depression during ST walking when compared to non-depressed controls. We observed, however, higher levels of HbO_2 in individuals with depression during ST. One possible reason for the increased activity could be that individuals with depression had to concentrate more during walking compared to non-depressed individuals. This concurs with a previous study investigating PFC activity during walking in older adults (Eggenberger et al., 2016). In the latter study, a reduced PFC activity was found after a cognitive-motor training intervention, which was accompanied with improved executive functioning. Contrary to these findings, hypo frontality in depression has been well-documented in previous studies (George et al., 1995; Matsuo et al., 2005; Soares and Mann, 1997). A difference between these previous studies and the current work is that hypo frontality was observed at rest or while performing cognitive activities without concomitant physical activity. This as opposed to our study where people were walking during cognitive task performance. The discovery of similar activation patterns on both the left and right sides of the brain in both non-depressed and depressed individuals in both single and dual task conditions, was unexpected. Previous research had consistently indicated left prefrontal cortex hypoactivity in individuals with depression (Galynker et al., 1998; Martinot et al., 1990; Okada et al., 2003). Furthermore, our results showing elevated HbO_2 values during DT walking compared to ST walking, align with previous research conducted in healthy older participants using fNIRS. In a recent meta-analysis, it was shown that when participants walked while subtracting there was a notable increase in HbO_2 concentration in the PFC (Lapanan et al., 2023).

5. Clinical implications

Our findings can be used to raise awareness about modifiable depression-associated physical and neurobiological markers which could then be treated and, hence, alleviate the burden in people with depression, e.g., through more valid diagnosis and identifying treatment response. A patient currently is considered to be in remission from depression when his or her acute emotional symptoms have abated, however, residual physical symptoms increase the likelihood of relapse (Trivedi, 2004). Similarly, recent advances in prevention reveal that the promotion of physical health, physical activity, and emotion regulation strategies bear potential for successful treatment, however, it is currently not clear what the most effective intervention characteristics and potentially moderating factors are (Loechner et al., 2018). The parameters identified in our study, particularly cognitive and motor alterations, could be considered as starting point for developing such innovative non-pharmacological treatment approaches.

Heart rate variability (HRV), prefrontal cortex oxygenation, and executive functions can be modified through interventions in individuals with depression, while gait is a factor that is associated with depression and can also be a target for intervention and change (Stahl et al., 2021). For instance, exercise and specific training can improve prefrontal cortex function and executive functions (Schattin et al., 2016). Additionally, therapies like medication or neuromodulation have been shown to increase HRV and improve executive functions in patients with depression (Noda et al., 2022). Gait speed and patterns are also modifiable, with interventions like exercise potentially improving gait (Schattin et al., 2016).

6. Limitations and future research

As with all studies our investigation also has some limitations that

should be mentioned. One of the weaknesses of cross-sectional studies includes the inability to make a causal inference. The study design is better suited for generating hypotheses for further research, such as a longitudinal study, which is needed to establish causality. Furthermore, this type of studies often needs to select a sample of subjects from a large and heterogeneous study population making results susceptible to sampling bias (Wang and Cheng, 2020). Awareness of the limitations requires for example specific considerations for the analytical approach. Our study aimed to establish a new way of diagnosing depression, in which a diagnostic model was fed with multiple factors associated with depression in combination to estimate the probability that depression is present at the time of prediction. Such an approach preferably uses modern shrinkage or penalization procedures, such as LASSO regression, rather than stepwise selection methods and *P* value-based criteria (Wang and Cheng, 2020). For readers to be able to assess the potential usefulness of our findings and enable the risk of bias to be adequately assessable, we adhered to the STROBE statement (von Elm et al., 2007) and STARD guideline (Bossuyt et al., 2015).

7. Conclusion

Based on our findings further research and assessments in diverse neuropsychiatric patient populations is warranted to assess the diagnostic relevance of our multiparametric assessments. This should be done with a focus on enhancement of validity of a clinical diagnosis complemented with the presented assessments. Regarding the intended use and clinical role of the test battery longitudinal interventional studies that try to improve depression with a pre-test post-test design should be designed to assess causality between the measured symptoms and changes in disease status. Based on the current findings such an approach is warranted.

Ethics approval and consent to participate

The Ethics Committee of Eastern Switzerland (Ethikkommission Ostschweiz (EKOS)) approved this study (Project-ID 2022–02,261, EKOS 22/204). All participants signed a written informed consent.

Consent for publication

N/A.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Data availability

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher upon request.

CRediT authorship contribution statement

Eling D. de Bruin: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Nadine Buffat:** Writing – review & editing, Project administration, Investigation, Data curation. **Emanuel Brunner:** Writing – review & editing, Supervision, Resources, Investigation, Funding acquisition. **Davy Vancampfort:** Writing – review & editing, Supervision, Methodology, Investigation. **Stefan Büchi:** Writing – review & editing, Supervision, Conceptualization. **Josef Jenewein:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Patrick Eggenberger:** Writing – review & editing, Methodology, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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