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Peripheral body temperature rhythm is associated with suicide risk in major depressive disorder: a case-control study

Xin Ma ,[1,2] Jing Cao,[2] Hailin Zheng,[2] Xinchun Mei,[2] Meijuan Wang,[2] Haoran Wang ,[3] Yu Shuai,[2] Yuan Shen [2,4]

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XM and JC contributed equally.

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[1]School of Medicine, Tongji University, Shanghai, China
[2]Department of Psychiatry, Tongji University Tenth People's Hospital, Shanghai, China
[3]Department of Computer Science, Tongji University, Shanghai, China
[4]Anesthesia and Brain Research Institute, Tongji University, Shanghai, China

Correspondence to
Yu Shuai; 1225994300@qq.com

Dr Yuan Shen; kmshy@tongji.edu.cn

ABSTRACT

Background Patients with major depressive disorder (MDD) may have an abnormal peripheral body temperature rhythm, but its relationship with suicidal risk and the response to treatment with antidepressants remain unknown.

Aims This study aimed to investigate the feature of peripheral body temperature in patients with MDD and its relationship with suicide risk before and after treatment with antidepressants.

Methods This is a prospective case-control study. Patients diagnosed as MDD were enrolled into MDD group. Healthy subjects who matched in terms of gender, age and body mass index were enrolled into normal control (NC) group. The 24-hour peripheral body temperatures were monitored by *TM' Holter* the next day after assessment. Patients with MDD were re-assessed after a 2-week treatment with antidepressants. All temperature data were fitted into cosine curves by *Python*.

Result There were 41 patients with MDD, and 21 NC participants enrolled and completed the baseline assessments before the treatment. Patients with MDD were further divided into subgroup of with suicide risk or without suicide risk. In patients with MDD, the mesor of peripheral body temperature rhythm was higher in both patients with (36.17 (0.30)) and without suicide risk (36.22 (0.27)) than the mesor in NC participants before treatment (35.84 (0.38), Z=11.82, p=0.003, Kruskal-Wallis test). The phase-delay of temperature before treatment was greater in patients with MDD with suicidal risk (4.71 (1.68)) in comparison with those without suicidal risk (3.05 (2.19)) and NC participants (3.19 (1.82), Z=9.68, p=0.008, Kruskal-Wallis test). Moreover, phase-delay of temperature was associated with suicide risk in patients with MDD before treatment (OR=1.046, 95% CI: 1.009 to 1.085, p=0.015, unadjusted; OR=1.080, 95% CI: 1.020 to 1.144, p=0.009, adjusted by age and sex).

Conclusion Patients with MDD might have abnormal peripheral body temperature. The abnormal phase-delay of peripheral body temperature may indicate suicide risk in patients with MDD, depending on validation in large-scale cohorts.

INTRODUCTION

Major depressive disorder (MDD) is among the most prevalent and potentially fatal mental disorders worldwide.[1] The cost of MDD in the USA had reached US$99 billion in 2010 and is estimated to cost US$188–US$200 billion within a decade.[2] Moreover, MDD is the most common causes of suicide in adults, which forms the predominant part of the disease burden of MDD.[3] However, the diagnosis of MDD has to rely on behavioural assessments rather than biomarkers owing to the lack of knowledge of the mechanism. Moreover, there remains no reliable method to differentiate subjects at high risk of suicide. This big gap impedes the diagnosis of MDD and prevention of suicide.

Evidence has been continuously suggesting that disruptions of circadian rhythms are the main chronobiological abnormality of MDD, including body temperature, sleeping, hormone producing and other biological activities.[4] In particular, patients with MDD usually suffer from disturbed body temperature rhythm.[5] Abnormal body temperature rhythm, such as reduced amplitude, significant phase-delay and low average body temperature for several days, has been observed in patients with MDD.[6] It is suggested that the abnormal body temperature of MDD might root in functional disturbance of circadian organisation.[7] Moreover, core features of depression including anhedonia and low mood are also thought to stem from disruptions in the circadian system.[4] Treatments that work on circadian cycle, for example, light therapy and agomelatine (a melatonin receptor agonist) can improve depressive symptoms.[8] Therefore, body temperature rhythm is a physical parameter that closely correlates with depressive mood. Nevertheless, whether this abnormality in body temperature rhythm could be normalised after treatments and its relationship with depressive symptoms, especially with suicide risk, remains largely unknown. We, therefore, set out a case-control study to investigate the features of abnormal peripheral

temperature rhythm before and after antidepressant treatment among patients with MDD, particularly the association of abnormal peripheral temperature rhythm with suicide risk. The study aimed to determine whether antidepressant treatment could normalise peripheral body temperature rhythm and explore the relationship between peripheral body temperature rhythms as well as suicide risk among patients with MDD.

The hypotheses of the study were: (1) patients with MDD might have abnormal parameters of peripheral body temperature rhythm, which were associated with depressive symptoms; (2) patients with MDD with suicide risk might have discriminative features of peripheral body temperatures differing from patients with MDD without suicide risk, and (3) the abnormal parameters of peripheral body temperature rhythm among patients with MDD could be normalised after the treatment by antidepressants.

METHODS

Study population

A total of 114 patients in the Department of Psychiatry at Shanghai Tenth People's Hospital were screened from April 2017 to December 2017. Patients were included into MDD group if they were: (1) 18–50 years of age; (2) had >5 years of education; (3) diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[9], and (4) stopped taking antidepressants for at least 2 months if it was not the first episode. Patients were excluded from MDD group based on the following criteria: (1) if they were diagnosed of other mental disorders (eg, schizophrenia, bipolar disorder or any type of anxiety disorders) according to the DSM-IV; (2) prior diagnosis of neurological diseases (eg, Parkinson's diseases or multiple sclerosis) according to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[10]; (3) were pregnant or in lactation (for female patients only); (4) had attempted suicide in the current episode, and (5) had diseases, which may influence peripheral body temperature, for example, fever caused by any reason.

Healthy participants were included in normal control (NC) group if they were: (1) 18–50 years of age, and (2) had >5 years of education. Participants were excluded from NC group based on the following criteria: (1) prior diagnosis of other mental disorders according to DSM-IV; (2) prior diagnosis of neurological diseases (eg, Parkinson's diseases or multiple sclerosis) according to ICD-10, and (3) had diseases, which may influence peripheral body temperature, for example, fever caused by any reason. All of participants >50 years were excluded to avoid the confounding effects of low level of oestrogen to temperature in female participants.[11]

Assessments at the enrolment (baseline)

The assessments at the enrolment (baseline) were performed by two psychiatrists (YS and JC). The demographic characteristics included age, height, weight, sex, education and body mass index (BMI); psychological assessments consisted of Hamilton Depression Scale 17 items (HAMD-17), Hamilton Anxiety Scale (HAMA), Patient Health Questionnaire (PHQ-9), Mood Disorder Questionnaire (MDQ) and Pittsburgh Sleep Quality Index (PSQI).

HAMD-17 scale is a clinician-administered instrument consisting of 17 questions. It is used to measure the severity of depressive symptoms.[12] It includes five factors/dimensions[13]: (1) anxiety/somatoform: containing items of anxiety-psychic, anxiety-somatic, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis and loss of insight; (2) weight: loss of weight; (3) cognitive impairment: feelings of guilt, suicide and agitation; (4) retardation: depressed mood, genital symptoms, work and activities and retardation; (5) insomnia: insomnia-early, insomnia-middle and insomnia-late. The suicide risk was determined by the third item of HAMD-17: with suicide risk (item score ≥3) and without suicide risk (item score <3). This cut-off value has been commonly used in previous studies.[14] Moreover, decrease of total score of HAMD-17 was used to evaluate the effectiveness of antidepressants: partial response and response were defined as HAMD-17 reductive ratio of 25% and 50%, respectively.[15]

HAMA is a clinician-administered scale consisting of 14 symptom-defined items, which includes both psychological and somatic symptoms. Each item is scaled by a 0–4 Likert-type score ranging from 0 (asymptomatic) to 4 (severe); and a score of 13 or above is defined as having anxiety symptoms.[16]

PHQ-9 is a self-report questionnaire accessing depressive symptom frequency in recent 2 weeks, comprising nine depressive symptoms directly linked to DSM-IV criteria of MDD. Each symptom is scaled by a 0–3 Likert-type score: 0 = 'never', 1 = 'several days (≤7 days)', 2 = '>7 days' and 3 = 'almost every day'. The total score of PHQ-9 ranges from 0 to 27 points and severity of depression increases as total score increases.[17]

MDQ is a screening questionnaire used to exclude possible bipolar disorder.[18] MDQ consists of 13 items being classified into three sections: symptom endorsement (section 1), symptom clustering (section 2) and severity of problem caused (section 3). The participants were excluded for potential bipolar disorder if: (1) score of section 1 is >7 and two or more symptoms occurred at the same time; (2) the functional impairments due to symptoms are 'moderate' or 'severe'.

PSQI is used to assess the sleep quality of participants over the past month.[19] The questionnaire consists of nine questions. All nine questions could be divided into seven components: sleep quality, sleep latency, sleep time, sleep efficiency, sleep disorder, hypnotic drug and day function. PSQI total scores is the sum of the seven components ranging from 0 to 21. The higher PSQI score indicates lower quality of sleep.

Peripheral body temperature monitoring

The 24-hour peripheral body temperature was collected by continuous actigraphy monitoring system designed by Well Diagnostics (Shanghai, China). A temperature sensor (TM' Holter, MH-80N) was fixed on axilla by medical gel and peripheral body temperature was monitored every 5 s continuously through 24 hours. Then these data were transferred to Well Baby, an application which had been downloaded on mobile phones of each participant. The data were stored in the flash memory automatically via Bluetooth interface and then transmitted to work station of Well Baby via internet. To avoid manipulated temperature variation during data collection, participants were required to avoid doing exercise or using heating facilities (eg, electric blanket or warming paste). Using air conditioning was allowed.

The temperature rhythm was evaluated by cosine curve, which was processed by *Python* V.3.6.0 (Wang, Well Diagnostics). Four parameters, including amplitude (circadian peak value), mesor (mean value), nadir (point of valley value) and phase-shift (the displacement of the acrophase, including phase-advance and phase-delay), were generated by *Python* to describe the feature of cosine curve of body temperature.

Antidepressive treatment

The only treatment in the study involved the use of antidepressants, which were fully determined by clinicians. All patients with MDD (n=41) started taking antidepressants the next day of enrolment after 24-hour peripheral body temperature had been recorded. Among them, a total of 25 participants were treated by selective serotonin reuptake inhibitors: sertraline (n=12, 50–100 mg/d), citalopram (n=3, 20 mg/d), escitalopram (n=6, 10 mg/d), paroxetine (n=2, 20 mg/d) and fluoxetine (n=2, 20 mg/d). The other 16 patients were treated by serotonin and norepinephrine reuptake inhibitors: venlafaxine (n=11, 75 mg/d) and duloxetine (n=5, 40 mg/d).

No intervention was given to NC participants.

Assessments after treatment (follow-up)

Patients with MDD and NC participants were re-evaluated by the same assessment tools (HAMD-17, HAMA, PHQ-9, MDQ and PSQI). All of them accepted the second peripheral body temperature monitoring by the same method at follow-up.

Statistical analysis

Continuous variables were presented as mean and SD; discontinuous variables were presented as median and IQR (25% percentile–75% percentile). Sex was presented as number (n) and percentage (%). Kruskal-Wallis test was used to test differences in demographic, clinical and temperature characteristics of different groups by time: at the baseline and after the treatment. The χ^2 *test* was used to determine differences in categorical variables (eg, sex). Paired-samples t-test was used to determine longitudinal difference of clinical and temperature characteristics of each group. Spearman's correlation adjusted by age and sex was used to determine the relationship between depressive symptoms and body temperature rhythms. Mann-Whitney U test was used to determine difference of temperature characteristics between luteal phase and follicular phase among female patients with MDD. Logistic regression was used to determine the association between body temperature rhythms and suicide ideation.

A receiver operating characteristic (ROC) curve was performed to determine the optimal cut-off point of phase-delay for identifying suicide risk in patients with MDD. Then the predictive probability of certain feature was evaluated by the area under the curve (AUC). The optimal cut-off was obtained according to Youden Index (sensitivity+specificity−1).

All analyses were performed using IBM SPSS V.20.0 (IBM, Armonk, New York, USA) with $p<0.05$ as the significance level.

RESULT

Characteristics of participants

A total of 83 patients with MDD were screened (figure 1). Among them, 29 were excluded owing to: (1) psychosis history (n=20) and (2) Refused to use temperature monitor (n=9). A total of 54 eligible patients with MDD were enrolled for baseline assessments. Then 13 of them failed to complete the baseline assessment owing to invalid temperature data as a result of either drop of monitors (n=7) or using heating facilities (n=6). Thus, a total of 41 patients with MDD were included for analysis before the treatment. Among them, 22 patients with MDD were categorised into group with suicide risk and the other 19 patients were categorised into the group without suicide risk. The mean age of all patients with MDD was 31.3 (6.4) years, with 22.0% participants being male. After a 2-week treatment with antidepressants, 17 patients with MDD dropped out at follow-up assessments owing to the following reasons: (1) declined follow-up assessments (n=16), and (2) suicide after enrolment (n=1). In the end, data from 24 patients with MDD were used for analysis after the treatment.

A total of 31 NC participants were screened, 10 of them were excluded for withdrawal of the consent (n=5) or refused to use temperature monitor (n = 5) (figure 1). A total of 21 participants were enrolled for baseline assessments. The mean age of NC participants was 28.8 (3.6) years, 42.9% participants were male (table 1). After an interval of 2 weeks, 21 participants were re-assessed and 6 participants were excluded owing to invalid temperature data (n=6). Thus, there were 15 NC participants who completed the follow-up assessment.

The demographic characteristics of patients with MDD and NC participants are shown in table 1. In general, both patients with MDD with and without suicide risk had lower level of education than NC participants (median (IQR): 16 (15–16), 16 (13–16) and 17 (16–19), for patients with MDD with suicide risk, without suicide risk and NC

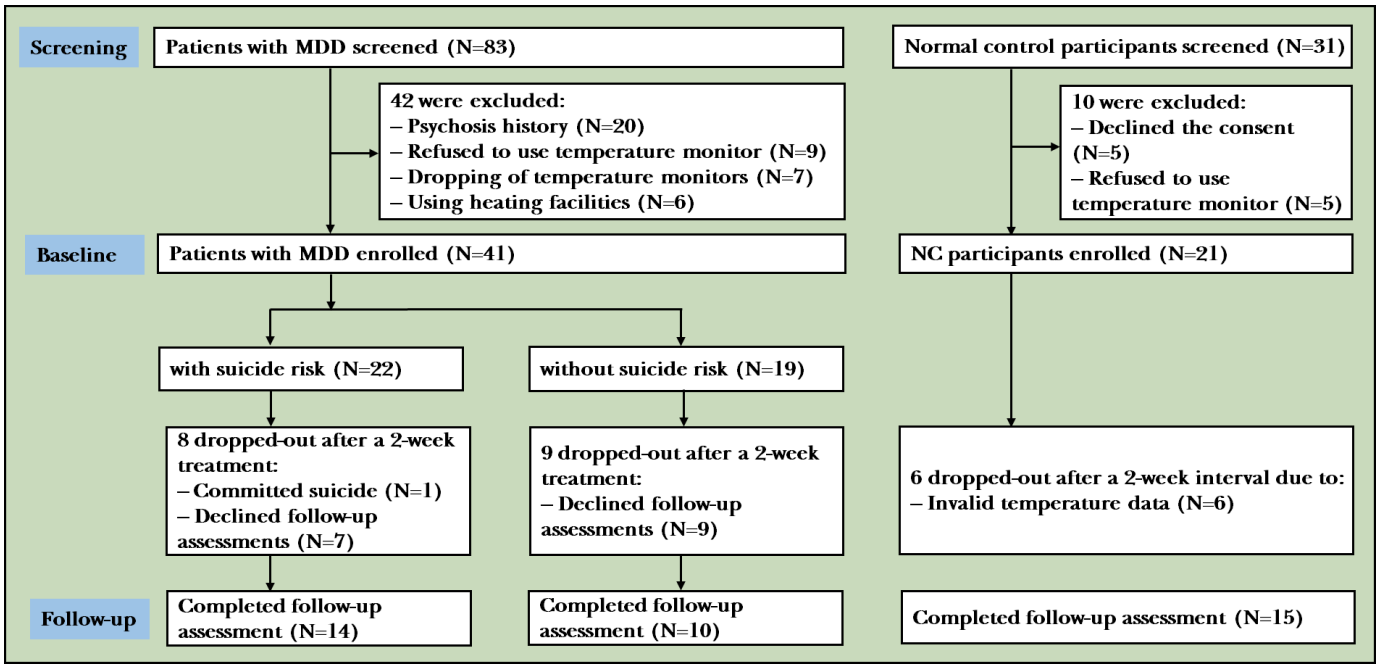

Figure 1 Flowchart. A total of 83 patients with major depressive disorder (MDD) and 31 normal control (NC) participants were initially screened, among which 41 patients with MDD (including 22 patients with suicide risk and 19 patients without suicide risk) and 21 NC participants were enrolled at the baseline analysis. After 2 weeks, 17 patients with MDD (including 8 patients with suicide risk and 9 patients without suicide risk) and 6 NC participants were dropped out for not completing follow-up assessments. Thus, data from 24 patients with MDD and 15 NC participants were used for the final data analysis.

participants, respectively, Z=7.47, p=0.024, Kruskal-Wallis test). There was difference in age among the three groups: patients with MDD with suicide risk (28.7 (4.2)) and NC participants (28.8 (3.6)) were younger than patients with MDD without suicide risk (34.3 (7.2), Z=9.05, p=0.011, Kruskal-Wallis test). There were no significant differences in height, weight, BMI and sex among patients with MDD with or without suicide risk and NC participants (table 1).

Psychological assessments of participants

Patients with MDD had higher scores in all scales at baseline than participants of NC, including HAMA, HAMD-17, PHQ-9, MDQ and PSQI (table 1). The median course of current episode of patients with MDD was 9 months and the IQR from 2 to 36 months. A proportion of 58.3% patients with MDD had combined anxiety symptoms.

After the treatment, scores of all scales in patients with MDD decreased significantly (online supplemental table 1). Among 24 patients with MDD assessed at follow-up, 20 out of 24 (83.3%) achieved partial response (HAMD reductive ratio ≥ 25%) and 10 out of 24 (41.6%) achieved response (HAMD reductive ratio ≥ 50%) to the treatment by antidepressants.

Features of peripheral body temperature of patients with MDD

Before the treatment, both patients with MDD with suicide risk (36.17 (0.30)) and without suicide risk (36.22 (0.27)) had higher mesor than NC participants (35.84 (0.38), Z=11.82, p=0.003, Kruskal-Wallis test). There was no difference in mesor between patients with MDD with and without suicidal risk before the treatment (36.17 (0.30) vs 36.22 (0.27), Z=0.41, p=0.681, Mann-Whitney U test). Moreover, patients with MDD with suicide risk had greater phase-delay (4.71 (1.68)) than patients with MDD without suicide risk and NC participants (3.05 (2.19) and 3.19 (1.82), for MDD without suicide and NC, respectively, Z=9.68, p=0.008, Kruskal-Wallis test) (table 1).

After the treatment by antidepressants for 2 weeks, the mesor which increased in patients with MDD before the treatment tended to decrease and the difference among three groups disappeared (table 2). Nevertheless, the change in mesor was not significant within group of patients with MDD with suicide risk (36.08 (0.31) vs 36.00 (0.35), Z=1.29, p=0.220, paired-samples t-test) and without suicide risk (36.17 (0.29) vs 36.31 (0.25), Z=−1.55, p=0.156, paired-samples t-test) (online supplemental table 1). Similarly, the difference in phase-delay among the three groups disappeared after treatment while the change was not significant within the groups after the treatment. There was no difference in other temperature parameters among the three groups before or after the treatment (p>0.05).

Association of peripheral body temperature and depressive symptoms

Before treatment, the amplitude was negatively associated with factor score of insomnia (R=−0.346, p=0.031, adjusted by age and sex, Spearman's correlation, n=41); the nadir was negatively associated with factor score of insomnia (R=−0.332, p=0.039, adjusted by age and sex); the phase-delay was positively associated with factor score

Table 1 Demographic and clinical characteristics and features of peripheral body temperature of patients with MDD (with suicide risk and without suicide risk) and NC participants before the treatment

Assessments	MDD with suicide risk (n=22)	MDD without suicide risk (n=19)	Normal participants (n=21)	χ^2/Z	P value
Demographic characteristics, (mean (SD))					
Age (years)	28.7 (4.2)	34.3 (7.2)	28.8 (3.6)	9.05	**0.011**
Height (cm)	163.4 (5.6)	165.3 (5.8)	165.1 (7.2)	0.96	0.619
Weight (kg)	58.0 (10.4)	59.5 (12.1)	58.4 (8.7)	0.32	0.854
BMI (kg/m^2)	21.8 (3.5)	21.6 (3.1)	21.3 (2.6)	0.03	0.987
Education (years), median (IQR)	16 (15–16)	16 (13–16)	17 (16–19)	7.47	**0.024**
Sex, male, n (%)	3 (13.6)	6 (31.6)	9 (42.9%)	4.54	0.103
Clinical characteristics, (median (IQR))					
HAMA	14.5 (12.8–18.0)	13.0 (12.0–15.0)	2.0 (0.5–2.5)	45.03	**<0.001**
HAMD-17	25.5 (22.0–29.0)	21.0 (18.0–24.0)	2.0 (1.0–3.0)	41.67	**<0.001**
PHQ-9	21.0 (17.8–23.3)	13.0 (12.0–15.0)	2.0 (1.0–3.0)	46.28	**<0.001**
MDQ	3.0 (2.0–4.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)	13.93	**0.001**
PSQI	13.5 (11.0–17.0)	13.0 (10.0–15.0)	3.0 (2.0–5.0)	39.63	**<0.001**
Features of peripheral body temperature, (mean (SD))					
Mesor	**36.17 (0.30)***	**36.22 (0.27)†**	35.84 (0.38)	11.82	**0.003**
Amplitude	0.38 (0.29)	0.38 (0.20)	0.31 (0.14)	4.09	0.130
Phase-delay	**4.72 (1.68) ‡**	3.05 (2.19)	3.19 (1.82)	9.68	**0.008**
Nadir	5:00 (2:53)	5:12 (4:41)	7:27 (5:33)	2.88	0.237

Sex was calculated by χ^2 test, statistic value: χ^2. Others were calculated by Kruskal-Wallis test, statistic value: Z; p: MDD versus NC at baseline. The differences were determined with significance level of 0.05 and statistically significant results in the table are in boldface.
*Patients with MDD with suicide risk versus NC participants: Z=2.81, p=0.015; patients with MDD with suicide risk versus patients with MDD without suicide risk: *Z*=0.41, p=0.681.
†Patients with MDD without suicide risk versus NC participants: Z=3.11, p=0.006.
‡Patients with MDD with suicide risk versus MDD without suicide risk: Z=2.52, p=0.035; patients with MDD with suicide risk versus NC participants: Z=−2.81, p=0.015.
BMI, body mass index; HAMA, Hamilton Anxiety Scale; HAMD-17, Hamilton Depression Scale 17 items; MDD, major depressive disorder; MDQ, Mood Disorder Questionnaire; NC, normal control; PHQ-9, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

of cognitive impairment (R=0.434, p=0.006, adjusted by age and sex) and the mesor was positively associated with the factor score of retardation (R=0.347, p=0.030, adjusted by age and sex). These associations disappeared after the 2-week treatment with antidepressants. There was no association between temperature parameters and other factor scores or total score of HAMD-17 either before or after the treatment (p>0.05) (online supplemental table 2).

Association between peripheral body temperature and suicide risk

The association of peripheral body temperature and suicide risk before treatment was analysed by logistic regression. As it showed, the phase-delay of peripheral body temperature was significantly associated with the suicide risk of patients with MDD before treatment (OR=1.046, 95% CI: 1.009 to 1.085, p=0.015, unadjusted; OR=1.080, 95% CI: 1.020 to 1.144, p=0.009, adjusted by age and sex, n=41) (table 3). There was no association between other temperature parameters and suicide risk (p>0.05).

ROC analysis was then performed to determine the optimal cut-off point of phase-delay of peripheral body temperature before the treatment for the identification of suicide risk. The AUC was 0.696 (95% CI: 0.523 to 0.869, p=0.032, n=41). An optimal cut-off point of 4.345 was obtained by Youden Index (sensitivity+specificity−1). Employing this defined cut-off point of phase-delay, 17 out of 22 patients with MDD with suicide risk were identified as having suicide risk. The sensitivity of the identification was 0.773 (77.3%). Among 19 patients with MDD without suicidal risk, 13 of them were identified as not having suicide risk and 6 of them were identified as having suicide risk. The specificity of identification was 0.684 (68.4%).

Features of peripheral body temperature of female patients with MDD

Given that peripheral body temperature is influenced by ovulation in female patients, we compared the temperature features of all female participants (n=32) between follicular phase and luteal phase. The mesor of peripheral

Table 2 Peripheral temperature characteristic of MDD participants with suicide risk, without suicide risk and normal participants after the treatment

Temperature characteristic	with suicide risk (n=14)	without suicide risk (n=10)	Normal participants (n=15)	Z	P value
Clinical characteristics, (median (IQR))					
HAMA	9.5 (5.8–14.0)	6.5 (5.8–8.3)	1.0 (1.0–3.0)	27.20	**<0.001**
HAMD-17	14.0 (10.0–17.5)	10.0 (7.8–11.0)	2.0 (1.0–3.0)	28.55	**<0.001**
PHQ-9	13.5 (7.8–19.3)	4.0 (1.8–7.0)	2.0 (1.0–2.0)	24.96	**<0.001**
MDQ	2.0 (1.0–3.3)	2.0 (2.0– 2.0)	2.0 (1.0–2.0)	1.01	0.605
PSQI	11.5 (7.8–12.8)	8.5 (4.8–11.8)	3.0 (2.0–5.0)	20.71	**<0.001**
Features of peripheral body temperature, (mean (SD))					
Mesor	36.00 (0.35)	36.31 (0.29)	36.02 (0.34)	4.68	0.096
Amplitude	0.27 (0.17)	0.36 (0.17)	0.31 (0.15)	1.32	0.518
Phase-delay	4.05 (1.93)	3.01 (2.09)	2.821 (2.00)	4.33	0.115
Nadir	7:23 (4:19)	6:11 (6:57)	5:47 (5:28)	3.97	0.138

Temperature characteristics were calculated by Kruskal-Wallis test, statistic value: Z; p: with suicide risk versus without suicide risk at baseline. The differences were determined with a significance level of 0.05 and statistically significant results in the table are in boldface. HAMA, Hamilton Anxiety Scale ; HAMD-17, Hamilton Depression Scale 17 items; MDQ, Mood Disorder Questionnaire; PHQ-9, Patient Health Questionnaire ; PSQI, Pittsburgh Sleep Quality Index.

body temperature increased after ovulation in female in both patients with MDD (36.11 (0.21) vs 36.38 (0.29), Z=−2.49, p=0.011, Mann-Whitney U test) and NC participants (35.75 (0.56) vs 36.03 (0.26), Z=−1.54, p=0.149, Mann-Whitney U test). Moreover, mesor during follicular phase in female patients with MDD was higher in comparison with female NC participants (36.11 (0.29) vs 35.75 (0.26), Z=−2.33, p=0.017, Mann-Whitney U test) (online supplemental table 3).

DISCUSSION

Main findings

This study demonstrates that patients with MDD have disrupted rhythm of peripheral body temperature and the phase-delay of temperature rhythm is associated with suicide risk in patients with MDD. The abnormal rhythm of peripheral body temperature in patients with MDD tends to diminish with the improvement of depressive symptoms after the treatments by antidepressants.

Previous studies have reported a higher mesor of core body temperature (eg, oral temperature and anal temperature) in patients with MDD.[20] Intensive treatments such as electric convulsive treatment and deep brain stimulation could diminish the abnormal rhythm of body temperature in patients with MDD.[20] In this study, patients with MDD show significantly higher mesor before the treatment. Moreover, after a 2-week treatment with antidepressants, the disturbed rhythm of body temperature of patients with MDD tended to be normalised. Meanwhile, these results indicate that patients with MDD have abnormal features of peripheral body temperature rhythm, which might be independent of improvement of depressive symptoms at the early stage of the treatment. These features might be potential physical indicators of patients with MDD. However, it remains unknown whether the abnormal peripheral body temperature will totally be normalised with remission achieved, pending for further investigation in future.

Table 3 Logistic regression of peripheral body temperature and suicide risk in patients with major depressive disorder before the treatment (n=41)

	Unadjusted		Adjusted by age and sex	
Peripheral body temperature	OR (95% CI)	P value	OR (95% CI)	P value
Mesor	1.037 (0.792 to 1.357)	0.793	0.793 (0.498 to 1.262)	0.327
Amplitude	0.942 (0.605 to 1.466)	0.790	0.635 (0.281 to 1.436)	0.276
Phase-delay	1.046 (1.009 to 1.085)	**0.015**	1.080 (1.020 to 1.144)	**0.009**
Nadir	1.000 (0.997 to 1.003)	0.903	1.000 (0.995 to 1.005)	0.876

The differences were determined with a significance level of 0.05 and statistically significant results in the table are in boldface.

Body temperature is highly sensitive to the disruption of homeostasis, which could be influenced by various factors including mental status, physical condition and sleep cycle.[20–22] In this study, we find that amplitude of peripheral body temperature is associated with the severity of insomnia. Decreased amplitude of circadian rhythm in patients with MDD have been reported by previous studies.[23] Consistently, Barbini *et al* found that patients with more severe depression symptoms have lower amplitude of body temperature rhythm than healthy control.[24] The mechanism of decreased amplitude of circadian rhythm in patients with MDD remains unknown. It is considered to be associated with the desynchrony between endogenous rhythm and exogenous input signal rhythm, which has been identified in patients with MDD.[25] Consistently, we found that the decreased amplitude of circadian rhythm disappeared after insomnia improved. Moreover, we find that this change tends to diminish with the remission of depressive symptoms. These evidences indicate that lower amplitude could be an indicator of disturbed circadian rhythm and severity of insomnia of patients with MDD, which can be determined after further studies.

Phase-shift (including phase-advance and phase-delay) has been reported to be associated with severity of depression and the degree of cognitive dysfunction in patients with MDD.[26] But it remains unknown whether the indication of severity points to suicide risk of patients with MDD. In this study, we find that phase-delay of temperature rhythm in patients with MDD is significantly associated with suicide risk. The detection of suicide risk is difficult because it is usually concealed by patients with MDD because of shamefulness or other reasons. Investigations have been carried out to look for objective markers indicating suicide risk of patients with MDD. For instance, lower level of monoamine (5-hydroxytryptamine (5-HT) and 5-hydroxyindole acetic acid) in cerebrospinal fluid (CSF) is highly associated with suicide risk in patients with MDD.[27] However, the examination of CSF markers is invasive and expensive. Body temperature as a non-invasive and non-expensive parameter has been found to be closely associated with 5-HT level in CSF.[28] It is speculated that the relevance of temperature and 5-HT level probably relies on the regulating centre of circadian rhythm located in suprachiasmatic nucleus, which mainly consists of serotonin neurons and norepinephrine neuron. In this study, 77.3% patients with MDD who have suicide risk are identified as 'with suicide risk' using the optimal cut-off (4.345) of phase-delay. These findings suggest that phase-delay of peripheral temperature might serve as a potential non-invasive indicator to suicide risk of patients with MDD instead of CSF 5-HT level; this can be further investigated with a larger sample size and longer period of intervention. It would be of special significance to suicide prevention with the validation of this non-invasive and non-expensive marker.

LIMITATIONS

There are several limitations in this study. First, the period of intervention is relatively too short, which may lead to false negative results. Nevertheless, the primary aim of this study is to explore the association of the peripheral body temperature and suicide risk in patients with MDD before the treatment. Concerning the reaction to the treatment, previous studies suggest that 2 weeks could be an interval for evaluating response to antidepressants.[29 30] Second, the drop-out rate is relatively high. Nevertheless, we compared demographic and temperature characteristics between followed-up and dropped-out groups and no differences were found (online supplemental table 4). Third, factors affecting peripheral body temperature are hard to be avoided completely, even though detecting peripheral temperature is much more practical relative to detecting other parameters. Thus, findings from current studies are of clinical significance.

IMPLICATIONS

MDD is among the most prevalent and potentially fatal mental disorders worldwide. There remains no biological marker to differentiate subjects at high risk of suicide. Results of our study suggest that patients with MDD have abnormal features of peripheral temperatures. Particularly, those who have greater phase-delay of peripheral body temperature rhythm are under higher suicide risk. Such findings may help clinicians to recognise the subjects with high risk of suicide and provide intervention to prevent suicide attempt.

CONCLUSION

In conclusion, temperature rhythm is an accessible biological characteristic associated with MDD. Phase-delay of peripheral body temperature is a potential indicator of suicide risk of patients with MDD, and further studies with larger-scale cohorts and longer period are required.

Contributors XMa: manuscript preparation and data analysis; JC: clinical assessments; HZ: data collection and analysis; XMei: data analysis; MW: clinical assessments; HW: data modelling; YShuai: data collection and behavioural assessments; YShen: study design, quality control and manuscript preparation.

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ORCID iDs
Xin Ma http://orcid.org/0000-0001-7263-6284
Haoran Wang http://orcid.org/0000-0002-4622-0119
Yuan Shen http://orcid.org/0000-0002-7811-1478

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Xin Ma majored in clinical medicine in Tongji University and received a bachelor's degree in July 2020. In September 2020, she began her study for a master's degree of psychiatry under the direction of professor Yuan Shen, Tongji University, Shanghai. During the course of her study, she participated in research done in the field of psychiatry on topics such as circadian rhythm of major depressive disorder and association between psychological resilience and work performance. Moreover, she won scholarships from Tongji University for four consecutive years. Her research interests during postgraduate period include the affective disorder, function of postoperative delirium, brain β-amyloid and retinal nerve fiber layer (RNFL) β-amyloid.