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Elevated brain pulsations in depression: insights from a pooled ultrasound cohort study

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Excessive brain tissue pulsations (BTP), measured by ultrasound, have been associated with depression and are hypothesized to contribute to brain damage in this population at risk for cerebrovascular lesions. However, previous research has been limited by small sample sizes. To address this issue, our study pooled data from three separate investigations, resulting in the largest cohort of depressed participants with BTP measurements to date. We analysed 123 participants (74 individuals with depression and 49 healthy controls) using ultrasound tissue pulsatility imaging (TPI) to assess resting BTP. Results showed that both MeanBTP and MaxBTP were significantly associated with depression, as determined by multiple linear regression models that included age, sex and blood pressure as covariates. Additionally, we found that age, sex and diastolic blood pressure were significant predictors of BTP. Specifically, BTP decreased with age, was higher in men, and was more strongly predicted by diastolic blood pressure than by systolic blood pressure. In this large cohort, we replicated the association between depression and increased BTP, supporting the notion that elevated BTP may be a potential mechanism underlying brain damage over time. Our findings suggest that TPI could serve as a valuable surrogate marker for brain health in clinical practice.

1. Introduction

Recent advancements in ultrasound (US) technology now allow for the precise measurement of brain pulsations. Indeed, the brain pulsates within the cranial cavity and moves by a few micrometres with a period of about 1 s, primarily influenced by heartbeats transmitted to the brain parenchyma through the arteries. Our team and others have used US measurement of brain tissue pulsations (BTP) to investigate factors associated with BTP amplitude variations. A wide range of physiological and pathophysiological conditions, including blood pressure [1], ageing [2], brain volume [3,4], cerebrovascular lesions [5,6], visual and auditory stimulation [7,8], neural activity [2], orthostatic hypotension [1], hypocapnia [9] and psychiatric disorders like neuroticism and depression [10–12], have been linked to BTP. However, most previous studies had relatively small sample sizes, and the determinants of BTP amplitude remain incompletely characterized.

Depression is a severe mental disorder not only because of its dramatically high prevalence worldwide [13] but also because it exposes to pathophysiological complications such as cerebrovascular lesions and stroke [14–16]. The mechanisms underlying the depression–cerebrovascular lesion link are not fully understood, but we have proposed that elevated BTP amplitudes may contribute to brain tissue damage over time. Indeed, our previous research observed larger BTP amplitudes in depressed participants compared to healthy controls and those with past but not current depression [17]. In addition, we observed that BTP amplitudes decreased after two months of successful antidepressant therapy [18]. Moreover, changes in BTP can be used as a maker for treatment response in depressed participants expose to 1 h of nitrous oxide, a gas with rapid antidepressant properties [19]. Yet, these studies were limited by small sample sizes and required replication in larger cohorts. Larger studies would also allow for investigation of potential confounding factors using more robust statistical models.

This study aims to pool data from three studies conducted at the same location, all of which utilized identical BTP measurement procedures and included participants with depression. Our objectives were threefold: (i) to replicate the finding of increased BTP amplitude in depression with greater statistical power than previous studies, (ii) to investigate potential confounding factors that might influence the association between depression and BTP, and (iii) to confirm the previously observed relationships between BTP, age, sex and blood pressure.

2. Methods

2.1. Participants and study design

Data were pooled from three studies (the EMPHILINE study [17], the M-PULSE study [8] and the BIORESA study [18], respectively, NCT02026622, NCT03867422 and NCT03118193 on clinicaltrials.gov) performed in the same location of the Clinical Investigation Centre of the Hospital of Tours, France. All these three studies included the same US procedure to measure BTP amplitude (notably the same US device and the same operators) at rest and had the same inclusion criteria for depressed participants and healthy controls.

A total of 123 participants were included in the analyses among which 74 were considered depressed and 49 healthy controls. All depressed patients had to meet the DSM-IV criteria for a major depressive disorder as assessed by a trained psychiatrist with a severity score > 20 on the Montgomery–Åsberg Depression Rating Scale (MADRS). All control subjects were recruited from the local community and from the records of the Clinical Investigation Centre of the Hospital of Tours, France. Non-inclusion criteria for the three trials included any history of psychiatric or neurological disorders, pregnancy and legal guardianship. In the first two trials, individuals with a history of severe cardiovascular disease or currently taking beta-blockers or psychotropic medications were also excluded. Informed consent was obtained from all participants in each of these trials, and the local human ethics committee approved the research protocols.

2.2. Ultrasound protocol

The US protocol was extensively described elsewhere [19]. It was carried out on an Antares medical scanner (Siemens Healthcare, Germany) by a biophysics technician trained for tissue pulsatility imaging (TPI). Transcranial acquisitions were conducted using a PX4-1 phased-array transducer (Siemens Healthcare; 1.82 MHz emission frequency, 70° field of view, 112 × 3 elements (1.5D). Measurements were taken through the right temporal bone window, with the probe placed perpendicular to the skull and stabilized by a mechanical holder to minimize artefacts from both operator and subject movements. Subjects were instructed to maintain a seated position. They were asked to stay still and breathe normally. The US scanner was first set to Doppler mode for transcranial Doppler acquisition. Colour doppler was utilized to align the US beam with the right middle cerebral artery (MCA). The pulsatility index (PI—ratio of the difference between maximal and minimal velocities over mean velocity) and the maximum and mean velocities of the MCA were obtained and automatically calculated by the scanner from a 10 s Doppler sequence. Subsequently, the US scanner was switched to Echo-B mode for TPI measurements centred on the MCA. To reduce US attenuation, the acquisition depth was adjusted between 3 and 9 cm. This configuration enabled the exploration of the circle of Willis and a transversal slice of the temporal hemispheres. For each participant, the protocol included four 10 s acquisitions that were repeated with an acquisition fame rate of 30 images s^{-1} (total of 297 frames). The US scanner provided direct access to beam-formed radiofrequency (RF) lines, which were utilized to estimate BTP. The data were then transferred for offline analysis using MATLAB software (MathWorks, USA).

Our method, as described below, evaluates the z-axis component of brain displacements. The z-axis is perpendicular to the US probe surface while the x-axis extends along the surface of the probe. The US firing sequence consists of a series of M broad-view-focused pulsing events transmitted sequentially. Between each firing, the transmission (TX) steering angle θ (i.e. the angle of propagation relative to the normal surface of the transducer) is incrementally adjusted to cover a range of M angles throughout the entire series of pulsing events. For each focused transmission TX at a specific θ angle, beam-formed IQ data lines are generated from echoes captured by the transducers. At each time point t, we independently estimate brain tissue motion at all pixel positions. For a particular pixel of interest located on a US line identified by the transmit angle θ, we utilized the temporal lag-one autocorrelation algorithm [20] to determine the phase shift $\Delta\varphi$ between successive complex IQ data. We used the modified version [21] of the Doppler equation used for vector flow estimation, where $\vec{V}$ is the Doppler tissue velocity, λ the US wavelength, T the IQ temporal discretization interval, $\vec{n}_{TX}$ the direction of the US propagation in transmit mode TX, and $\vec{n}_{RX}$ the direction of the US RX beamforming.

$$\Delta\Phi = \frac{2\pi T}{\lambda}\left(\vec{V} \cdot \vec{n}_{TX} + \vec{V} \cdot \vec{n}_{RX}\right) \tag{2.1}$$

In our application, these two vectors' directions are identical and $\vec{n}_{TX} = \vec{n}_{RX} = \vec{n}$ with $\vec{n} = (\sin\theta, \cos\theta)$. Thus, the phase shift $\Delta\varphi$ estimated by our algorithm expressed:

$$\Delta\Phi = \frac{4\pi T}{\lambda}\vec{V} \cdot \vec{n} = \frac{4\pi T}{\lambda}(V_x \sin\theta + V_z \cos\theta) \tag{2.2}$$

This Doppler phase shift $\Delta\varphi$ is angle θ dependent and is also influenced by the lateral tissue velocity V_x. Within our applied setting, the circulation of blood causes the brain to swell, primarily resulting in a radial displacement. Given that the US probe is positioned perpendicular to the skull, and thus nearly perpendicular to the outer surface of the brain, the V_x tissue velocity component aligned with the x-axis in equation (2.2) is minimal, and therefore, it was disregarded. Consequently, the expression or Doppler phase shift can be simplified to $\Delta\Phi = \frac{4\pi T}{\lambda}V_z\cos\theta$, enabling us to calculate the component V_z of the brain tissue velocity along the depth axis from z-axis displacement. u_z is obtained from the cumulative summation of V_z in the temporal domain.

$$V_z = \frac{\lambda}{4\pi T}\frac{1}{\cos\theta}\Delta\Phi \tag{2.3}$$

We acquired a three-dimensional matrix of BTP, consisting of axial displacements u_z (x, z, t) along the z-axis, x-axis and time t. Subsequently, we examined the temporal evolution of BTP at each position within the two-dimensional plane.

Two criteria were used to eliminate artefacts and emphasize physiological signals, which are presumed to be stable in terms of periodicity and amplitude. The first criterion investigated the periodicity of brain pulsations and involved the ratio of the second maximum peak to the central peak (SMP/CP) of the temporal autocorrelation function of each kernel. Records were validated if the SMP/CP ratio exceeded 0.6 and then subjected to the second criterion. The second criterion assessed the difference in amplitudes between pulsations in each curve. The cumulated standard deviation (CSTD) of the pulsations was calculated to assess data dispersion and normalized to the peak-to-peak amplitude (U_{mean}) of the mean temporal curve. Records were validated if the CSTD/U_{mean} ratio was less than 0.25; otherwise, they were rejected. The thresholds for the two criteria were based on previous studies [5,17].

From this final matrix, two curves, MaxBTP and MeanBTP, were extracted, corresponding to the curve with the maximum mean peak-to-peak amplitude (averaged between cycles) and the average of all curves in the matrix, respectively. MaxBTP and MeanBTP represent the pulsatility of the largest artery (i.e., MCA) and the mean pulsatility across the entire acquisition region, respectively.

2.3. Statistical analyses

Clinical variables were described and compared according to the presence or absence of a depressive state. Quantitative variables were described using means and standard derivations and compared using a Student's t-test. Qualitative variables were described by numbers and percentages and compared using a chi-square test.

We conducted two multiple linear regression analyses to examine the association between depression (independent variable) and MeanBTP (dependent variable in the first regression model) and MaxBTP (dependent variable in the second regression model). To control for potential confounding factors, we included age, sex, systolic blood pressure and diastolic blood pressure as covariates in both models. We evaluated these two models in the entire sample and in separate analyses for depressed and healthy control subgroups. The symbols β and t, as presented in table 2, denote the estimated coefficients of the regression models.

Finally, we tested associations in the depressed sub-group between MeanBTP and MaxBTP with depression severity (the MADRS) and duration of the episode, using Pearson's correlation. We also compared MeanBTP and MaxBTP between antidepressant users and non-users in the depressed sub-group using a Student's t-test. Statistical analysis was performed using JASP statistical software, version 0.18.1.

3. Results

Demographic and clinical characteristics are shown in table 1. There was no significant difference between the depressed and control groups regarding age, sex, systolic and diastolic blood pressure. Univariate comparison found that MeanBTP was significantly greater in the depressed group, whereas there was no significant difference in MaxBTP (figure 1).

Results of the multiple linear regressions are shown in table 2. In the whole sample, MeanBTP (F = 3.187, p = 0,010) was positively associated with depression (t = 2.685, p = 0.008) and sex (male) (t = 2.697, p = 0.008), whereas MaxBTP (F = 7.489, p<0,001) was positively associated with depression (t = 2.220, p = 0.028) and sex (male) (t = 2.602, p = 0.010) and negatively associated with age (β = −0.266, p = 0.003) and diastolic blood pressure (β = −0.370, p = 0.008). In the depressed sub-sample, the only significant association was between MaxBTP and age (β = −0.288, p = 0.018), although there were statistical trends for a negative association between MaxBTP and diastolic blood pressure (β = −0.331, p = 0.082) and for a positive association between MaxBTP and sex (male) (t = 1.693, p = 0.095). In the healthy controls sub-group, MeanBTP was positively associated with sex (male), whereas MaxBTP was negatively associated with age (β = −0.272, p = 0.049) and diastolic blood pressure (β = −0.432, p = 0.048). There was also a statistical trend for a positive association between MaxBTP and sex (male) (t = 1.851, p = 0.071).

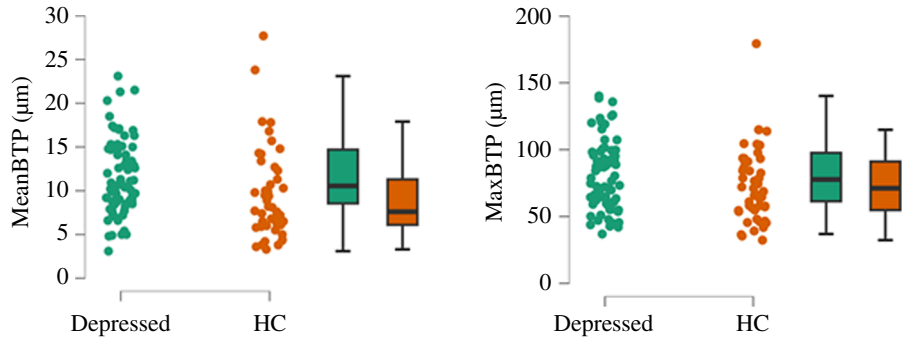

Figure 1. Scatter plots and box plots of MeanBTP (left) and MaxBTP (right) in the depressed (green) versus healthy control (HC; orange) groups.

Table 1. Comparisons of the clinical and US characteristics between depressed and healthy control groups. Values are expressed as mean (standard derivation) or *n* (%). Comparisons were performed with *t*-tests (quantitative data) and chi-squared tests (qualitative data). DBP, diastolic blood pressure; MDE, major depressive episode; MADRS, Montgomery–Åsberg Depression Rating Scale; SBP, systolic blood pressure.

	depressed (*n* = 74)	controls (*n* = 49)	*p*-value
age (years)	33.5 (13.3)	33.3 (11.7)	0.955
sex (female)	61 (82.4%)	40 (81.6%)	0.910
SBP (mmHg)	122.0 (14.2)	124.1 (16.1)	0.460
DBP (mmHg)	75.5 (11.5)	73.3 (10.3)	0.291
MADRS score	30.5 (4.9)	—	—
duration of MDE (weeks)	26.0 (33.0)	—	—
antidepressant use	11 (14%)	—	—
meanBTP (µm)	11.5 (4.3)	9.4 (5.2)	0.014
maxBTP (µm)	81.1 (25.9)	73.8 (27.4)	0.142

Table 2. Results of the multiple linear regression analyses that were conducted to examine the associations between MeanBTP or MaxBTP (dependent variables) and depression (in the whole sample only), age, sex, systolic blood pressure (SBP) and diastolic blood pressure (DBP) (independent variables) across the whole sample and within depressed and control subgroups. MDE: major depressive episode; MADRS: Montgomery–Åsberg Depression Rating Scale; BTP: brain tissue pulsations.

	whole sample (*n* = 123)		depressed sub-sample (*n* = 74)		controls sub-sample (*n* = 49)	
	MeanBTP	MaxBTP	MeanBTP	MaxBTP	MeanBTP	MaxBTP
depression	$t = 2.685$, $\mathbf{p = 0.008}$	$t = 2.220$, $\mathbf{p = 0.028}$	—	—	—	—
age	$ß = 0.117$, $p = 0.907$	$ß = -0.266$, $\mathbf{p = 0.003}$	$ß = 0.037$, $p = 0.777$	$ß = -0.288$, $\mathbf{p = 0.018}$	$ß = -0.007$, $p = 0.958$	$ß = -0.272$, $\mathbf{p = 0.049}$
sex (male)	$t = 2.697$, $\mathbf{p = 0.008}$	$t = 2.602$, $\mathbf{p = 0.010}$	$t = 1.474$, $p = 0.145$	$t = 1.693$, $p = 0.095$	$t = 2.108$, $\mathbf{p = 0.041}$	$t = 1.851$, $p = 0.071$
SBP	$ß = 0.085$, $p = 0.563$	$ß = 0.177$, $p = 0.194$	$ß = -0.187$, $p = 0.342$	$ß = 0.182$, $p = 0.309$	$ß = 0.310$, $p = 0.210$	$ß = 0.174$, $p = 0.459$
DBP	$ß = -0.116$, $p = 0.431$	$ß = -0.370$, $\mathbf{p = 0.008}$	$ß = 0.048$, $p = 0.818$	$ß = -0.331$, $p = 0.082$	$ß = -0.213$, $p = 0.343$	$ß = -0.432$, $\mathbf{p = 0.048}$

In the depressed sub-sample, we found no association between MeanBTP or MaxBTP and MADRS (respectively, $r = 0.014$, $p = 0.909$ and $r = 0.055$, $p = 0.642$) or duration of the episode (respectively, $r = -0.185$, $p = 0.114$ and $r = 0.032$, $p = 0.784$). There was also no significant difference in either MeanBTP or MaxBTP between antidepressant users versus non-users (respectively, 11.0 (4.3) versus 11.6 (4.3), $t = 0.437$, $p = 0.663$ and 70.4 (26.8) versus 83.0 (25.5), $t = 1.495$, $p = 0.139$).

4. Discussion

In this pooled US data study, we successfully replicated the finding of increased brain pulsations in depression within a large cohort. Consistent with previous research, univariate analyses showed that MeanBTP was significantly higher in depressed participants compared to healthy controls, while MaxBTP did not show a significant association. However, in multivariate analyses, which accounted for age, sex and blood pressure, MaxBTP became significantly associated with depression.

Additionally, the association between depression and MeanBTP was further strengthened when these covariates were included in the multivariate models.

Our results demonstrate a significant association between depression and brain pulsations, which is not solely attributable to age, sex or blood pressure, known factors influencing BTP [1,2,22]. Our results also suggest that the relationship between brain pulsations and depression is confounded by age, sex or blood pressure, in the way that these variables amplify the association between BTP and depression, potentially due to strong reciprocal correlations.

We replicated the previously reported effect of ageing on decreased brain pulsation amplitudes [2]. Notably, we observed a stronger association with MaxBTP compared to MeanBTP, across both the entire sample and the two subgroups. Previous research has indicated that ageing primarily impacts larger brain pulsations (MaxBTP) rather than average pulsations (MeanBTP), suggesting a greater influence on large arteries or brain parenchyma structure. However, it is essential to note that our study population primarily consisted of young adults, limiting our ability to assess the full impact of ageing in older individuals.

The influence of sex on brain pulsations remains relatively understudied. Our findings indicate a strong association between male sex and increased brain pulsation amplitudes in both the total sample and the control subgroup. While there was a statistical trend towards a similar association in the depressed subgroup for MaxBTP, it did not reach statistical significance. Given the higher risk of brain damage, such as stroke, in men compared to women during mid-life [23], our results suggest that larger brain pulsations in males may contribute to this increased risk.

Interestingly, MaxBTP was also associated with blood pressure, with diastolic blood pressure being a stronger predictor than systolic blood pressure. Previous findings demonstrated a strong negative correlation between BTP and diastolic blood pressure, particularly evident during orthostatic challenges where BTP consistently decreased with rising diastolic blood pressure while systolic blood pressure remained relatively stable [18,22]. These observations align with the previously described influence of pulse pressure on BTP. As diastolic blood pressure increases and systolic blood pressure remains constant, pulse pressure diminishes, consequently reducing brain pulsations. Conversely, a decrease in diastolic blood pressure can lead to increased pulse pressure and larger brain pulsations. This mechanism likely explains the negative association between diastolic blood pressure and MaxBTP.

We found no association between BTP and depression severity (as assessed by the MADRS), episode duration or antidepressant use. This could be attributed to insufficient statistical power or the absence of a dose–response relationship between BTP and depression severity. Our findings suggest that all patients with depression, regardless of symptom severity, may be at risk for brain damage. This implies a need for equal attention to both severe and mild depression in terms of potential brain health implications.

Limitations of this study include its cross-sectional design, which precludes us from causal inference. However, our previous longitudinal research observed a decrease in brain pulsations following clinical improvement in depression after a follow-up at two months. Conversely, brain pulsations remained elevated in patients with persistent depression, suggesting that elevated brain pulsations may serve as a state marker for depression. Additionally, the study's limitations include the inability to account for potential confounding factors such as brain volume, which has been linked to both depression and brain pulsations, due to the absence of magnetic resonance imaging (MRI) data in a significant portion of the participants.

5. Conclusion

In conclusion, our findings support the potential of US-based BTP measurement using TPI as a valuable marker of brain health, particularly in individuals at risk for brain damage, such as those with depression, who are susceptible to stroke, white matter lesions or brain atrophy. Furthermore, TPI shows promise as a bedside tool for assessing brain health in at-risk populations, including patients with neuropsychiatric disorders, complementing traditional methods like blood pressure monitoring and more costly, less accessible neuroimaging techniques such as MRI. The non-invasive, low-cost and easily implementable nature of TPI makes it an attractive option for routine brain health monitoring, enabling the early identification of individuals with excessive BTP. This could allow for timely interventions aimed at reducing BTP, potentially mitigating the detrimental effects of excessive brain pulsatility on brain tissue. However, longitudinal studies in the general population and among patients with various brain-related conditions are necessary to further substantiate these findings.

Ethics. This work did not require ethical approval from a human subject or animal welfare committee.

Data accessibility. Supplementary material is available at [24].

Declaration of AI use. We have not used AI-assisted technologies in creating this article.

Authors' contributions. U.C.: formal analysis, investigation, writing—original draft, writing—review and editing; Q.G.: supervision, validation, writing—review and editing; J.-Y.C.: formal analysis, software, supervision, validation, writing—review and editing; B.B.: data curation, methodology, supervision, validation, writing—review and editing; J.-P.R.: methodology, supervision, validation, writing—review and editing; V.G.: methodology, supervision, validation, writing—review and editing; W.E.-H.: supervision, validation, writing—review and editing; V.C.: supervision, validation, writing—review and editing; B.G.: supervision, validation, writing—review and editing; T.D.: conceptualization, investigation, supervision, validation, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

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