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Decrease in ultrasound Brain Tissue Pulsations as a potential surrogate marker of response to antidepressant

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ABSTRACT

Previous cross-sectional studies found excessive Brain Tissue Pulsations (BTP) in mid-life depression, which could constitute a mechanism of brain damage in depression. However, it remains unclear whether successful antidepressant therapy restores BTP amplitudes. In this prospective study, we investigated longitudinal changes in BTP in patients with a major depressive episode (MDE), among responders and non-responders to escitalopram.

Fifty-two individuals with a MDE, free of antidepressants at baseline, were included in an 8-week open-labeled escitalopram trial. Ultrasound Tissue Pulsatility Imaging (TPI) was applied to measure resting BTP and BTP reactivity in an orthostatic challenge, at baseline and at week 8.

TPI data were available for 48 participants divided into responders (n = 28, 58.3%) and non-responders (n = 20, 41.7%) according to change in the MADRS score. MaxBTP significantly decreased between baseline and week 8, only in responders. In addition, changes in MaxBTP during the orthostatic challenge were no longer significant at week 8 but only in responders.

Because excessive BTP constitutes a potential mechanism for brain damage, our results suggest that a successful pharmacotherapy could benefit patients to lower the risk of brain damage in individuals with depression, a population exposed to stroke, small arteries disease and brain atrophy. TPI could provide a surrogate biomarker to monitor antidepressant response and brain health in depression in clinical routine.

1. Introduction

Ultrasound (US) imaging techniques have been increasingly used in experimental studies to characterize the pathophysiology of psychiatric disorders, especially in depression (Siragusa et al., 2020b). These techniques include markers of vascular functioning (measure of carotid intima-media thickness for instance) or measures of brain perfusion (transcranial Doppler for instance) and results tend to support the involvement of peripheral and cerebral vascular dysfunction in depression (Siragusa et al., 2020b). Moreover, US imaging has advantages that include being non-invasive, portable and low cost, especially when compared to other imaging techniques such as Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET), and has the potential to provide biomarkers in clinical routine for treatment response and prognostic assessment in depression notably, a population exposed to stroke (Ford et al., 2021), small arteries disease (Khalaf et al., 2015) and brain atrophy (Ancelin et al., 2019).

Tissue Pulsatility Imaging (TPI) is a recent ultrasound technique similar to transcranial Doppler except that rather than focusing on only large arteries, it measures Brain Tissue Pulsations (BTP) on a large region of interest. TPI provides information on the mechanical properties of the brain parenchyma and a number of recent studies found that various physiological and pathophysiological conditions were associated with differences in BTP amplitudes (Ince et al., 2020a). Indeed, BTP amplitudes were found to lower with ageing (Angel et al., 2018), to increase in a visual task (Kucewicz et al., 2007), to decrease in a hyperventilation task (Kucewicz et al., 2008), to reduce while listening to certain music (Siragusa et al., 2020a), to vary with brain volumes

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(Desmidt et al., 2018) (Baranauskas et al., 2020) and with brain vascular lesions (Ternifi et al., 2014) (Ince et al., 2020b). In addition, our team has reported that BTP reactivity could be assessed during an orthostatic challenge, while showing that BTP amplitudes significantly dropped in upright position compared to supine position, but only in individuals with orthostatic hypotension compared to heathy volunteers (Biogeau et al., 2017). Finally, we have also reported evidence of excessive BTP amplitudes in middle-aged patients with major depressive episode (MDE) compared to controls and to remitted patients (Desmidt et al., 2017). However, this latter study was cross-sectional and no study has investigated changes over time in BTP with pharmacotherapy and it remains unclear whether response to antidepressant, typically defined as reduction of at least 50% of a depression scale, restores BTP amplitudes.

The goal of our study was to investigate longitudinal changes in BTP in patients with an MDE, among responders and non-responders involved in an 8-week escitalopram trial, a commonly prescribed first-line antidepressant. We sought to investigate changes between baseline (before treatment) and end of the trial, both in resting BTP and in BTP reactivity assessed during an orthostatic challenge, because BTP reactivity may inform on cerebral autoregulation, a physiological mechanism that was found impaired in depression (Luo et al., 2019).

2. Methods

2.1. Participants and study design

This study was approved by the French National Agency (2016-A01757-44) and an independent national research ethics committee (16/45–1043). The project was registered on the ClinicalTrials.gov website (NCT03118193) and was supervised by a clinical investigation monitoring committee (Inserm CIC1415). All of the patients signed informed-consent forms before enrolling in the trial.

Fifty-two outpatients aged 18–60 years were recruited for this ancillary study of the BIORESA project, the principal objective of which was to identify metabolomic signatures associated with response to antidepressant. The participants had to meet DSM-IV criteria for major depressive episode (MDE) and with a severity score >20 on the Montgomery–Asberg Depression Rating Scale (MADRS). Participants were also required to have no antidepressant treatment for at least 14 days before inclusion. Non-inclusion criteria included bipolar or schizophrenic disorder, neurological disorder, pregnancy and legal guardianship.

The study design was an 8-week open-labeled escitalopram trial with two evaluation visits, at baseline and at the end of trial (week 8). After informed consent, clinical and psychometric assessments were performed in the clinical investigation center. The clinical assessment included blood pressure, height and weight measurements. Psychometric assessments were performed by a trained psychiatrist (WEH or TD) and included the Mini International Neuropsychiatric Interview (MINI) for current and lifetime psychiatric disorders, including Major Depressive Disorder (MDD), and the MADRS for severity of depression. Escitalopram was prescribed by a senior psychiatrist (WEH or TD) after the baseline visit to be started the same day or the day after. The same clinical and psychometric assessments were repeated at visit 2 (week 8), including MADRS which was used to classify participants regarding their response status (participants with an MADRS reduction of 50% or greater were considered responders, otherwise non-responders).

2.2. Ultrasound protocol

Tissue Pulsatility Imaging data recording. US protocol included measures at rest and during an orthostatic challenge, in order to investigate changes both in resting BTP and in BTP reactivity as a potential marker for cerebral autoregulation. The methodology for TPI assessment at rest and during an orthostatic challenge has been extensively described elsewhere (Biogeau et al., 2017). Briefly, the whole US protocol was performed on an Antares medical scanner (Siemens Healthcare, Germany) by a trained investigator for TPI (PAD or BB) who was blinded for clinical status of the participants, including response status. Transcranial acquisitions were performed with a PX4-1 phased-array transducer (Siemens Healthcare; Germany). Measurements were performed through the right temporal bone window with the probe firmly maintained by a mechanical holder to reduce artifacts caused by the subject's movements including moving from supine to upright position. For resting measures, participants were asked to remain in the supine position, try not to move and breathe normally. Color Doppler was used to center the US beam on the right Middle Cerebral Artery (MCA). The US scanner was then switched to Echo-B mode to perform TPI measurements centered on the MCA. With this configuration, we explored the circle of Willis and a transversal slice of the temporal hemispheres.

For each subject, the whole protocol consisted of 8 acquisitions of 10s, repeated every minute, with an acquisition frame rate of 30 images/s (total of 297 frames). The first four acquisitions were used to compute resting BTP in the supine position. The four subsequent acquisitions were performed during an orthostatic challenge.

The US scanner provided direct access to beam-formed radio-frequency (RF) lines, which were used to estimate BTP. The data were then downloaded for offline analysis with MATLAB® software (MathWorks Inc., USA).

Tissue Pulsatility Imaging signal processing. The signal processing to extract measures of Brain Tissue Pulsations from Echo-B signals has been previously extensively described (Desmidt et al., 2017, 2018). Briefly, an1D-intercorrelation method between successive acquisition frames was used to estimate axial BTP. We use the maximum of the normalized intercorrelation coefficient, Txy/sqrt (TxxTyy), to estimate the delay between successive kernels on RF lines at a specific depth. A normalized correlation coefficient higher than 0.7 was required to validate the measurement. This ensure that the movement of the brain has not been too large between two successive acquisitions and that the US lines are similar enough to make a good measurement of the displacement. We chose a kernel size of 8 periods (176 points, 4 wavelengths, 3.3 mm at 1.82 MHz). Parabolic interpolation was performed around the 3 maximum points of the 1D correlation to make a subpixel estimate of the displacement. An overlap rate of 80% of the kernel was computed, resulting in a 660 μm spatial discretization. We then applied a bandpass filter (low cutoff = 0.75 Hz; high cutoff = 5.0 Hz) to focus on displacements related to heart rate and to filter out slow and fast movements due to, respectively, respiration and artifacts.

We obtained a 3D matrix of BTP: axial displacements along the z axis (RF lines), x axis (along the 112 elements of the probe) and time. We analyzed the temporal evolution of BTP at each position of the 2D plane. We used two criteria to filter out artifacts and focus on physiological signals. The first criterion consisted in the ratio of the second maximum peak over the central peak (SMP/CP) of the temporal autocorrelation function of each kernel. If the ratio SMP/CP was higher than 0.6, the record was validated and confronted to the second criterion. The cumulated standard deviation (CSTD) of the pulsations was calculated to inform on the data dispersion and was normalized to the peak-to-peak amplitude (Umean) of the mean temporal curve. If the ratio CSTD/Umean was lower than 0.25, the record was validated, otherwise rejected. The thresholds for the 2 criterion were based on previous studies (Desmidt et al., 2017; Ternifi et al., 2014).

From this final matrix, we calculated the root mean square of 2 curves, MaxBTP and MeanBTP, corresponding, respectively, to the curve with the maximum of the mean peak-to-peak amplitude (averaged between cycles) and to the averaging of all curves in the matrix. MaxBTP and MeanBTP thus correspond to the pulsatility of, respectively, the greater and the mean pulsatility in the whole region of acquisition.

2.3. The orthostatic challenge

The orthostatic challenge was performed according to the most recent international guidelines (Freeman et al., 2011). Blood pressure (BP) was measured with an automatic BP monitor (EDAN M3, Thames Medical, UK) with the armband wrapped around the right arm. After 5 min of supine rest, BP was measured in the supine position then immediately after standing (T0) and every minute for 3 min (T1min – T3min). The four ultrasound measures were manually synchronized with each BP measures.

2.4. Statistical analyses

Shapiro–Wilk's tests determined that BTP measures were not normally distributed and that the residuals of repeated measures ANOVAs, performed to investigate a time x group effect of pre- and post-treatment BTP measures in responders versus non-responders, were not all normally distributed. We therefore performed non-parametric analyses for paired measures within groups (Wilcoxon's test for resting BTP and Friedman's test with Bonferroni correction for changes in BTP reactivity in the orthostatic challenge).

3. Results

3.1. Clinical characteristics

Full TPI data were available for 48 participants (two participants were lost to follow-up, one participant committed suicide and TPI data were excluded for one participant because of a technical problem with the scanner), among which 28 responders (58.3%) and 20 non-responders (41.7%), based on change in the MADRS score. There was no significant difference in clinical characteristics or BTP measures between responders and non-responders, as shown in Table 1, except for MADRS at week 8 which was lower in responders compared to non-responders, as expected.

Table 1
Comparisons of the clinical and ultrasound characteristics between responders and non-responders. Values are expressed as the median (interquartile range) or n (%). Comparisons were performed with Mann-Whitney test (quantitative data) and chi-squared tests (qualitative data).

	Responders (n = 28)	Non-responders (n = 20)	Group comparison U or χ^2, p
Age (years)	25.4 (20.6)	20.8 (14.8)	U = 341.5, p = 0.198
Sex (female)	20 (71%)	15 (75%)	χ^2_1 = 0.075, 0.784
BMI (kg/m²)	24.1 (8.1)	22.6 (4.9)	U = 342, p = 0.195
SBP Baseline (mmHg)	121.5 (16.8)	118.0 (12.5)	U = 339.5, p = 0.213
DBP Baseline (mmHg)	74.0 (17.3)	74.5 (14.3)	U = 279.5, p = 0.992
SBP Week 8 (mmHg)	128.5 (27.0)	120.0 (18.5)	U = 355.0, p = 0.117
DBP Week 8 (mmHg)	73.5 (15.0)	70.0 (11.3)	U = 335.0, p = 0.249
Number of previous MDE	2.0 (1.5)	2.0 (1.0)	U = 97, p = 0.228
Duration of MDE (weeks)	12 (10.5)	16 (12.3)	U = 206.5, p = 0.123
MADRS Baseline	32.0 (8.8)	28.0 (5.8)	U = 347.5, p = 0.156
MADRS Week 8	8.0 (7.0)	22.0 (6.8)	U = 7.5, p < 10^{-4}
Escitalopram dosage Week 8 (mg)	10.0 (5.0)	10.0 (10.0)	U = 167, p = 503
MeanBTP Baseline (μm)	10.7 (4.9)	11.2 (5.8)	U = 259, p = 0.660
MaxBTP Baseline (μm)	87.2 (40.8)	90.9 (39.3)	U = 280, p = 1
MeanBTP Week 8 (μm)	11.3 (6.2)	12.7 (7.1)	U = 221, p = 0.217
MaxBTP Week 8 (μm)	70.3 (34.0)	77.3 (48.0)	U = 249, p = 0.517

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MDE: Major Depressive Episode; MADRS: Montgomery Asberg Depression Rating Scale; BTP: Brain Tissue Pulsations.

3.2. Resting BTP longitudinal changes

As shown in Fig. 1, we found no significant prospective change in MeanBTP between baseline and week 8 in either group (Z = −0.757, p = 0.449 in responders and Z = −1.369, p = 0.171 in non-responders). In contrast, MaxBTP significantly decreased between baseline and week 8, only in responders (Z = −2.118, p = 0.034), whereas we found no significant change in non-responders (Z = −0.523, p = 0.601).

3.3. BTP reactivity to orthostatic challenge

As shown in Fig. 2a, both MaxBTP and MeanBTP significantly decreased with the orthostatic challenge at baseline, in the two groups (χ^2 (4) = 24.059, p < 10^{-4} and χ^2 (4) = 23.170, p < 10^{-4} for MaxBTP and MeanBTP, respectively, in responders, and χ^2 (4) = 21.960, p < 10^{-4} and χ^2 (4) = 20.720, p < 10^{-4} for MaxBTP and MeanBTP, respectively, in non-responders). At week 8, the drop in MeanBTP remained significant with the orthostatic challenge in the two groups (χ^2 (4) = 19.514, p = 0.001 in responders and χ^2 (4) = 18.360, p = 0.001 in non-responders). In contrast, changes in MaxBTP with orthostatic challenge at week 8 were no longer significant in responders (χ^2 (4) = 5.114, p = 0.276), whereas it remains significant (in one difference, T1 min versus baseline) in non-responders (χ^2 (4) = 10.680, p = 0.030).

In parallel, BP increased during orthostatic challenge, with significant increases mostly occurring in diastolic blood pressure (DBP) at both baseline (χ^2 (4) = 24.059, p < 10^{-4} in responders and χ^2 (4) = 18.866, p = 0.001 in non-responders) and week 8 (χ^2 (4) = 43.441, p < 10^{-4} in responders and χ^2 (4) = 36.651, p < 10^{-4} in non-responders) in the two groups, as shown in Fig. 2b. Because of these significant changes in DBP, we investigated potential associations between DBP and MaxBTP and found that these measures significantly correlated at rest but only in responders at week 8 (rho = −0.521, p = 0.004). Noteworthy, we found no significant difference in DBP between baseline and week 8 in either group.

4. Discussion

The principal finding of our study was that the amplitude of the brain pulsatile movements, as assessed by MaxBTP, decreased after 8 weeks of escitalopram in patients with MDE who responded to treatment, whereas we found no significant changes in non-responders. While previous cross-sectional studies found excessive BTP in currently depressed patients compared to healthy controls and patients in remission (Desmidt et al., 2017), our finding suggest that successful pharmacotherapy restores BTP to a lower safer level.

BTP has multiple determinants including cerebral blood flow (CBF) reactivity and cerebrovascular tone (Kucewicz et al., 2007, 2008), blood pressure (Biogeau et al., 2017), neural activity (Angel et al., 2018), autonomous nervous system (ANS) activity (Siragusa et al., 2020a) and brain parenchyma structure such as brain volumes variations (Desmidt et al., 2018) (Baranauskas et al., 2020) or cerebrovascular lesions (Ternifi et al., 2014) (Ince et al., 2020b). Among these physiological mechanisms, serotoninergic agents, such as escitalopram, have shown effects on neural activity (Celada et al., 2013), ANS activity (Hong et al., 2017) and cerebrovascular tone (Côté et al., 2004). Possible explanations to account for reduction in BTP with successful pharmacotherapy therefore include modulation of the vascular tone of the MCA which may alleviate large variations in CBF reactivity via direct effect of serotonin on the vascular wall and/or an indirect modulation of neural and/or ANS activity on the vessel. Modulation of brain parenchyma

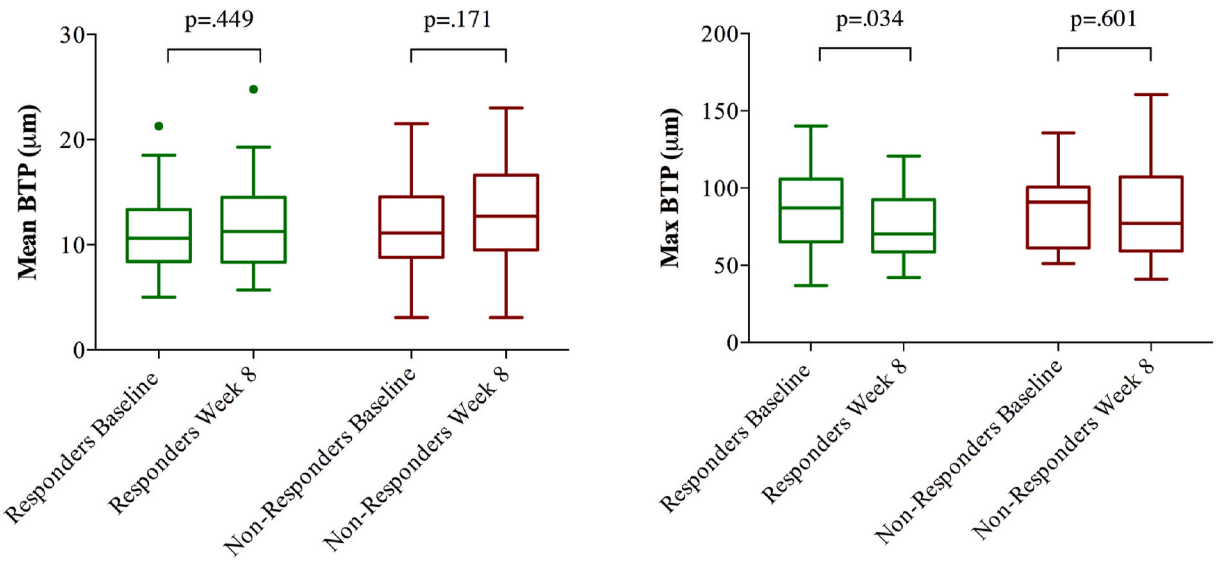

Fig. 1. Boxplots of the ultrasound measures (MeanBTP and MaxBTP) performed at baseline before treatment and after 8 weeks of escitalopram, in responders (green) and non-responders (red). MaxBTP was significantly lower after treatment in responders, whereas we found no significant difference in MeanBTP and in non-responders on any measure.

structure is less likely, notably because significant brain volumes changes would require more than 8 weeks of treatment and are more likely reflected by MeanBTP than MaxBTP, which reflects large brain pulsations due to large arteries, especially the MCA.

In addition, we found that MaxBTP reactivity, as assessed by changes in MaxBTP during an orthostatic challenge, was no longer significant after 8 weeks of escitalopram in responders. Interestingly, MaxBTP reactivity tends to be reduced after treatment in non-responders as well, although remaining statistically significant between supine and after 1 min of upright position. These results suggest an effect of pharmacotherapy to limit brain reactivity when exposed to mechanical stress, although a more significant effect requires both treatment and clinical remission. Previous studies have found impaired cerebral autoregulation in depression, understood as the ability of the cerebrovasculature to maintain a constant level of global brain perfusion despite varying arterial blood pressure (Luo et al., 2019). Our findings of significant drops in BTP during orthostatic challenge may relate to impairment in cerebral autoregulation and the absence of significant difference with successful treatment may indicate a restoration of an efficient mechanism of cerebral autoregulation in responders, which is consistent with the observation that no significant drop in MaxBTP occurred after successful treatment although the increase in DBP remained significant with orthostatic challenge. This observation also highlights the different potentials of MaxBTP and DBP as markers of antidepressant response, DBP appearing poorly discriminant compared to MaxBTP. Indeed, MaxBTP was both significantly different at rest and during orthostatic challenge after successful treatment, whereas DBP did not significantly differ at rest after treatment and remained significantly changed in orthostatic challenge after treatment. Interestingly though, DBP significantly correlated with MaxBTP but only in responders after treatment, suggesting that DBP is indeed a determinant of BTP but in normalized conditions, such as restored cerebral autoregulation, whereas in impaired cerebral autoregulation, such as in depression, the effect of DBP on MaxBTP is potentially modified by other factors that may include excessive sympathetic activity or impaired neuronal activity for instance.

Taken together, our results suggest potential benefits in successfully treating depression with antidepressant such as escitalopram as it may improve cerebrovascular reactivity and cerebral autoregulation. Moreover, because excessive BTP has been suggested to promote brain damage via direct mechanical stress on the brain parenchyma (Palta et al., 2019) and other mechanisms such as facilitating neuroinflammation (Troubat et al., 2020), lowering BTP with successful pharmacotherapy may participate to limit the risk of brain atrophy, white matter lesions and stroke, in a population particularly exposed to these complications (Ancelin et al., 2019; Ford et al., 2021; Khalaf et al., 2015).

Limitations of our study include that our data prevent implementing statistics such as linear general model to allow investigating time × group interactions, which would have constituted more powered statistics, because data were not normally distributed and because of the relatively small sample size. Besides, our sample was largely composed of young adults and conclusions can only be drawn for early-life depression whereas mid-life and late-life depression may be more influenced by ageing related physiology that tends to promote cerebrovascular impairments. The open-label design of the trial may also constitute a limitation since it is unknown if the decrease in MaxBTP may also occur with placebo. Furthermore, we only investigated pre- and post-treatment changes in BTP and it is unknown whether changes in MaxBTP occur earlier, within the first days of treatment, as a signal preceding clinical response. Future studies involving more frequent and earlier BTP measures may inform on the efficiency of TPI to guide clinical intervention. In addition, it is unclear why only MaxBTP, and not MeanBTP, showed significant change over time in responders. One possible explanation is that in young adults with depression the more significant effect of antidepressant and clinical remission is observed on large cerebral arteries whereas parameters more likely involved in MeanBTP such as small arteries reactivity or brain parenchyma changes may either be less involved in the effect of successful pharmacotherapy and/or may require a longer duration than 8 weeks to occur.

5. Conclusion

Our results have implications regarding the potential of using TPI to characterize changes in brain physiology related to the effect of antidepressant and symptomatic improvement in depression, as well as using TPI as a non-invasive, low-cost and easy-to-implement neuroimaging marker for monitoring brain health in depression, with the objective of lowering BTP and reducing the deleterious impact of excessive brain pulsatility, a mechanism that has been suggested to promote brain damage. However, the extend to how impairment in cerebrovascular reactivity, cerebral autoregulation or in brain pulsatility

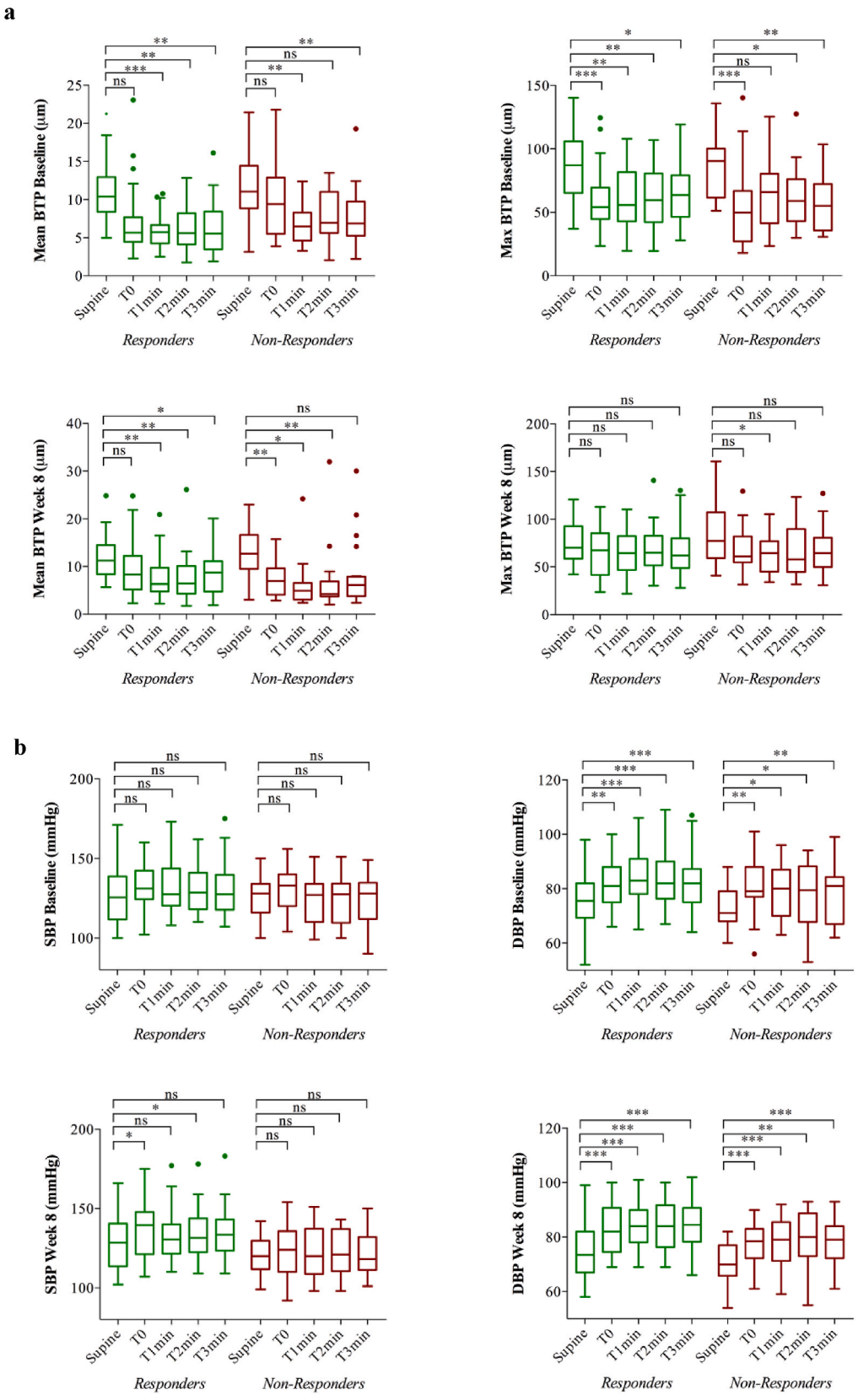

Fig. 2. Boxplots of the Mean and MaxBTP (Fig. 2a) and Systolic and Diastolic Blood Pressure (SBP, DBP, Fig. 2b) during the orthostatic challenge, at baseline before treatment and after 8 weeks of escitalopram, in responders (green) and non-responders (red). Only responders at week 8 showed no significant changes in MaxBTP at any time of the orthostatic challenge, whereas BTP measures significantly decreased during the challenge, at baseline in both group and in non-responders at week 8, at least at one time of the orthostatic challenge. Blood Pressure showed no drops during orthostatic challenge and in contrary tend to be elevated in upright position compared to supine, especially for DBP both at baseline and week 8 and in responders and non-responders. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ns = non-significant; after Bonferroni correction for multiple testing.

are deleterious for the brain remains speculative and large cohort investigating the risk of brain damage over time as a function of BTP values remain to be implemented.

Author statement

WEH designed the BIORESA study. TD, PAD, JPR and BB supervised the BIORESA TPI ancillary study. VG was in charge of the clinical investigation monitoring committee that supervised the study. PAD and TD gathered, analyzed and interpreted the data. TD wrote the article, which was critically reviewed by all authors.

Declaration of competing interest

TD reports personal fees from Janssen, Lundbeck, Otsuka and Eisai. WEH reports personal fees from Air Liquide, Eisai, Janssen, Lundbeck, Otsuka, UCB and Chugai. VC reports personal fees from Janssen and Bristol Myers Squibb. All other authors declare no competing interests.

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