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When Classical Music Relaxes the Brain: an experimental study using Ultrasound Brain Tissue Pulsatility Imaging

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ABSTRACT

Introduction: Recent evidence suggests that biomechanical parameters of the brain, such as Brain Tissue Pulsatility (BTP), could be involved in emotional reactivity. However, no study has investigated the impact of an emotional task on BTP. We used the ultrasound method of Tissue Pulsatility Imaging (TPI) to assess changes in BTP to exciting and relaxing classical music, in a musical perception task, as a validated paradigm to assess emotional reactivity.

Methods: 25 healthy volunteers were exposed via earphones to four 5-minutes musical excerpts (two exciting and two relaxing musical excerpts) presented in a randomized order and intersected by 5 silence periods. Measures of BTP, Heart Rate (HR) and Skin Conductance (SC) were collected during the entire task.

Results: The BTP significantly decreased with relaxing music compared to silence, and especially with the excerpt 'Entrance of the Shades' by Minkus. The HR and SC, but not Heart Rate Variability, were also decreased with relaxing music. We found no significant effect of exciting music.

Discussion: We report, for the first time, that classical relaxing music decreases the amplitude of the brain pulsatile movements related to cerebral blood flow and mechanical properties of the brain parenchyma, which provides further evidence of the involvement of BTP in emotional reactivity. In addition, we validate the use of TPI as a non-invasive, portable and low cost tool for studies in psychophysiology, with the potential to be implemented as a biomarker in musicotherapy trials notably.

1. INTRODUCTION

Musical perception tasks constitute a validated paradigm for the investigation of physiological changes related to emotional arousal (Hou *et al.*, 2017; Koelsch, 2014; Russo, Vempala, & Sandstrom, 2013; Salimpoor *et al.*, 2009; Gomez & Danuser, 2007). Reactivity of the autonomous nervous system (ANS) has been the most widely investigated physiological change with music perception (Koelsch & Jäncke, 2015). Robust findings include changes in heart rate (HR), notably showing that HR increases with exciting music compared to relaxing music (Koelsch & Jäncke, 2015). Exciting and relaxing music are also known as high and low energy and tension arousal dimensions of music (Eerola, & Vuoskoski, 2011). Changes in heart rate variability (HRV) tend to show a decrease in both the low frequency (LF) and the high frequency (HF) powers of the spectral analyses of HRV, when comparing music with silence and exciting music with less exciting music (Koelsch & Jäncke, 2015). In addition, skin conductance level (SCL) and blood pressure (BP), other physiological measures related to the ANS, were found to increase with fast-tempo music and decrease with slow-tempo music (Russo *et al.*, 2013).

Brain reactivity to music is a more recent matter of interest. Changes have been reported with music in brain structures such as amygdala, nucleus accumbens, hypothalamus, hippocampus, insula, cingulate cortex and orbitofrontal cortex, which are crucially involved in emotion, as shown in studies using functional Magnetic Resonance Imaging (fMRI) (Hou *et al.*, 2017; Martínez-Molina *et al.*, 2016; Koelsch, 2014). Studies using Positron Emission Tomography (PET) imaging have reported changes in cerebral metabolism with music perception, in regions similar to those found in fMRI studies (Blood & Zatorre, 2001; Lane *et al.*, 1997). More recently, studies using Transcranial Doppler (TCD), which provides functional measures of cerebrovascular response, including cerebral blood flow velocity (CBFV), reported an increase in large arteries CBFV with faster tempi and a decrease in CBFV with slower tempi during music perception (Bernardi *et al.*, 2009; Bernardi, Porta, & Sleight, 2006).

Recently, it has been suggested that other cerebral mechanisms related to certain brain mechanical properties could be involved in cognition and emotion. Chronic changes in cerebral biomechanics have been involved in various pathological processes such as cerebrovascular (Ternifi *et al.*, 2014; Tsao *et al.*, 2013) and neurodegenerative diseases (Smoliński & Członkowska, 2016; Wåhlin *et al.*, 2014; Sabayan *et al.*, 2012). More recently, it has been suggested that emotional disorders such as depression and the personality trait of neuroticism, which constitutes a risk factor for depression, also involved changes in cerebral biomechanics (Siragusa *et al.*, 2019, under review; Desmidt *et al.*, 2017). Furthermore, not only chronic variations but also acute and rapid changes in cerebral biomechanics have been found to occur with visual perception (Kucewicz *et al.*, 2007),

hyperventilation (Kucewicz *et al.*, 2008) and cognitive processing (Angel *et al.*, 2018). Finally, a close relation has been suggested, based on mathematical models, between cerebral biomechanics and rapidly changing density of neurons (Parker, 2017) as well as synaptic activity (Drukarch *et al.*, 2018), which may account for the link between cerebral biomechanics and cognition, perception and emotion. However, and while there is an emerging interest for cerebral biomechanics in emotional regulation, no study has currently investigated cerebral biomechanics in an emotional task such as a musical task.

Cerebral biomechanics include brain tissue pulsatility (BTP) which can be notably investigated using the recently developed Ultrasound (US) technique of Tissue Pulsatility Imaging (TPI). Indeed, our group and others have recently validated the use of TPI to investigate changes in BTP on healthy individuals (Kucewicz *et al.*, 2008; 2007) and in clinical populations (Biogeu *et al.*, 2017; Desmidt *et al.*, 2017; 2011). TPI is similar to TCD, except that rather than focusing on only large arteries, it relies on the Echo-B mode of a modern US scanner to measure the pulsatile movements of large brain regions, which allows a very high spatiotemporal level of detection (micrometers/millisecond) of brain volume changes related to pulsatile cerebral blood flow (CBF) and elastic properties of the tissue (Ternifi *et al.*, 2014). As a non-invasive, portable and reliable ultrasound technique, TPI may constitute a suitable tool for the investigation of cerebral biomechanical reactivity to various stimuli, although no study has currently implemented TPI in an experimental task involving emotional stimuli, such as classical music.

The goal of our study was to evaluate changes in Brain Tissue Pulsatility with music in a group of healthy individuals, so as to further investigate the role of cerebral biomechanics in emotional process. We designed a specific musical perception task based on the literature (Iwanaga *et al.*, 2005) to investigate change in BTP and in HR, HRV, SC as conventional markers for ANS-related peripheral reactivity, with both exciting and relaxing music compared to silence.

2. METHODS

2.1 Participants

Twenty-five individuals aged from 18 to 45 years were recruited from the local community and from the records of the Clinical Investigation Center of the Hospital of Tours, France. All eligible individuals were healthy and had no auditory impairment. Non-inclusion criteria for all subjects comprised: history of neurological (stroke, brain tumor, severe concussion, etc.) or psychiatric disorders (psychotic disorder, mood disorder, etc.), history of severe cardiovascular diseases (myocardial infarction, arrhythmia, etc.), current use of beta-blockers or psychotropics, or being a professional musician. A non-opposition letter for data collection was completed by a trained medical doctor (VG) for each subject willing to participate, and the study protocol was approved by the human ethical committee of Toulouse, France.

2.2 Clinical assessment

Clinical assessment included medical history, blood pressure measurement (immediately before US assessment) and psychometric assessment with the Barcelona Music Reward Questionnaire (BMRQ) for the evaluation of global sensitivity to music pleasure.

2.3 Musical Task

Musical task was performed immediately after a 5-minutes resting period in silence. Musical task was inspired by a previous study (Iwanaga *et al.*, 2005). The participant was seated on a fixed chair and connected to the US scanner and to the physiological equipment, which consisted of 3 ECG electrodes for heart rate recording and 2 electrodes for skin conductance recording placed on the first phalange of the forefinger and the middle finger of the left hand. In contrast to Iwanaga (Iwanaga *et al.*, 2005), a distracting task was used simultaneously to music presentation so as to control attention and visual perception, which consisted on presenting neutral images from the international validated image bank OASIS (Kurdi *et al.*, 2017). Images passed randomly for a random duration of 4 to 6 seconds on a screen located in front of the participant.

The Musical task consisted on presenting through earphones 2 excerpts of a 5-minutes exciting music and 2 excerpts of a 5-minutes relaxing music. Each musical excerpt was preceded and followed by a 5-minutes period of silence. Besides, all musical excerpts were randomly presented between subjects. After each excerpt, subject had to rate the grade of tension or relaxation elicited by the musical stimulus by pressing one of 7 different buttons on a keyboard (1= very little to 7= very much) for the evaluation of arousal (SAM, Self-Assessment Manikin).

The musical excerpts included those previously used by Iwanaga (Iwanaga *et al.*, 2005), namely 'Sacrificial Dance' from the 'Rite of Spring' by Igor Stravinsky for exciting music and

'Gymnopedie No.1' by Erik Satie in the version orchestrated by Claude Debussy for relaxing music. The two excerpts were different in style and in the principal musical features of rhythm, harmony, tempo and dynamics. The exciting stimulus was characterized by complex, accented and saccadic rhythms, dissonant harmonies and a wide range of dynamics (from 'piano' to 'fortissimo'). The relaxing stimulus was characterized by a slow tempo, simple rhythm with a slow pulsation, consonant harmonies and mostly 'piano' dynamics, with gentle 'crescendo'. Because the Iwanaga study found only a small effect on physiological measures with these two music excerpts, we decided to include two additional music excerpts in our protocol, one exciting and one relaxing. The novel exciting stimulus was the 'Allegro vivace' from the 'Ouverture' from the 'William Tell' by Gioacchino Rossini. The novel relaxing stimulus was 'La Bayadere, Act III- Entrance of the Shades' by Ludwig Minkus. The two novel excerpts are characterized by constant tempi and rhythms, homogeneous dynamics and consonant harmonies, while the most significantly different acoustic parameter between the two excerpts is the tempo (fast for exciting music and slow for relaxing music), which has been suggested to constitute the major determinant of physiological response to music (Bernardi, Porta, & Sleight, 2006).

2.4 Physiological measures processing

Physiological assessment was performed immediately after the psychometric assessment. Measures were collected after a 5-minutes resting period in seated position and included heart (HR), skin conductance (SC), and blood pressure (BP) at rest through a pressure cuff. Measures of HR and SC were collected continuously during the entire task (music excerpts and silence) by the Biopac system (MP150, BIOPAC Systems Inc. Goleta USA); a sampling rate of 1kHz was applied. Physiological measures were synchronized with stimuli presentation using the e-prime software (Psychology Software Tools, Sharpsburg USA).

For the extraction of HR, ECG signals were analyzed for each heart beat interval. The mean HR value was extracted for music and silence periods. Analyses for the extraction of heart rate variability (HRV) were performed in the frequency domain using a Fourier Transform algorithm. Three indexes of HRV were identified during music and silence periods: the low frequency power (LF), the high frequency power (HF), and their ratio (LF/HF). The frequency band for the LF component ranged from 0.04 and 0.15 Hz; the frequency band for the HF component ranged from 0.15 and 0.40 Hz.

Skin conductance responses (SCR) were estimated according to Kim, Bang & Kim (2004) guidelines. A threshold of 0.02 μ S was applied on the phasic level of skin conductance (SC) so as to characterize the SCRs, with a cutoff of 10% on detected SCRs, which allowed rejecting all responses with a detection threshold lower than 10% of the maximum of the response. Accepted

SCRs were characterized for their amplitude and were quantified according to their specificity. SCRs specificity was estimated according to musical stimulation or not, consistently with the *Handbook of Psychophysiology* (Cacioppo, Tassinary & Berntson, 2007). Specific SCRs (during music) were characterized with their magnitude, notably their amplitude weighted by non-specific responses (during silence) occurred after musical stimulation. Analyses were performed with the Acqknowledge[®]-5.0 software (BIOPAC Systems Inc.).

2.5 Ultrasound assessment

US protocol was performed on an Antares medical scanner (Siemens Healthcare, Germany) by a trained investigator for TPI (M.S.). Ultrasound acquisitions were performed every minute and were manually synchronized with stimuli presentations and physiological recordings. We relied on the methodology for TPI assessment that has been extensively described elsewhere (Desmidt *et al.*, 2017). Briefly, transcranial acquisitions were performed with a PX4-1 phased-array transducer (Siemens Healthcare; 1.82 MHz emission frequency, 70° field of view, 112 × 3 elements (1.5 D)). Measurements were performed through the right temporal bone window, which is the thinnest zone of the skull, with the probe positioned perpendicularly to the skull and maintained by a mechanical holder to reduce artifacts caused by the operator's and the subject's movements. Subjects were asked to remain in the seated position, try not to move and breathe normally.

The US scanner was first switched on Doppler mode for TCD acquisition. Color Doppler was used to center the US beam on the right MCA. The US scanner was then switched to Echo-B mode to perform TPI measurements centered on the MCA. To limit US attenuation, we adjusted the depth of acquisition between 3 and 9 cm. With this configuration, we explored the circle of Willis and a transversal slice of the temporal hemispheres.

For each subject, the protocol consisted of 5 acquisitions of 10 s repeated every minute for each period (4 musical excerpts and 5 silence periods) for a total of 45 acquisitions with an acquisition frame rate of 30 images/s (total of 297 frames). The US scanner provided direct access to beam-formed radiofrequency (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 Brain Tissue Pulsatility measures from Echo-B signals has been previously extensively described (Desmidt *et al.*, 2017). Briefly, axial BTP was estimated using a 1D-intercorrelation method between successive acquisition frames. The maximum of the normalized intercorrelation coefficient, $T_{xy}/\sqrt{T_{xx}T_{yy}}$, was used to estimate the delay between successive kernels on RF lines at a specific depth. The normalized correlation coefficient had to be higher than 0.7 to validate the measurement. A kernel size of 8 periods (176 points, 4 wavelengths, 3.3 mm at 1.82 MHz) was chosen. Parabolic

interpolation was performed around the 3 maximum points of the 1D correlation to improve the precision of the displacement measurement. With the Signal to Noise Ratio obtained after propagation through the skull, the noise level of BTP was 0.8 μm . For a better spatial discretization along RF lines, an overlap rate of 80% of the kernel was computed, resulting in a 660 μm spatial discretization. A bandpass filter (low cutoff= 0.75 Hz; high cutoff= 5.0 Hz) was then applied 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. The temporal evolution of BTP was analyzed at each position of the 2D plane (curves of the displacement as a function of time). We used two criteria to filter out artifacts and focus on physiological signals, supposed to be stable in terms of periodicity and amplitude. The first criterion was used to investigate the periodicity of the brain pulsations and 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. This threshold of 0.6 was chosen based on previous studies (Desmidt *et al.*, 2017; Ternifi, *et al.*, 2014). The second criterion was used to investigate the difference in amplitudes between pulsations in each curve. 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. This threshold of 0.25 was chosen based on the same reasons of the first criterion.

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.

2.6 Statistical Analyses

Due to a technical problem occurring during the experimental paradigm, one subject could not complete the protocol, so that only 24 subjects were included in the analyses. Participants' characteristics and arousal rating were reported using means and standard deviations. Shapiro-Wilk tests determined that US and physiological measures were normally distributed. BTP and peripheral physiological measures (HR, HRV, SCL, SCR) during the 5 silence periods were averaged to consider one value for silence. We applied two statistics model to account for 1) the effect of exciting music versus relaxing music versus silence (model 1, in which BTP and peripheral

physiological measures in the two exciting excerpts and in the two relaxing excerpts were averaged in one value for exciting music and relaxing music respectively) and for 2) the effect of each musical excerpt (model 2, silence versus the 4 musical excerpts separately). A repeated-measure General Linear Model (GLM) was applied to compare the means of BTP, HR, HRV, SCL and SCR between the 3 conditions (silence versus exciting music versus relaxing music, model 1) and between the 5 conditions (model 2). Statistical analyses were performed with the software SPSS version 24.

3. RESULTS

3.1 Clinical characteristics

The mean age of the participants was 26.5 ± 1.5 years-old with a majority of females (60%). The mean baseline systolic blood pressure was 129.1 ± 3.5 mmHg and mean baseline diastolic blood pressure was 74.2 ± 2.1 mmHg. No subject reported musical anhedonia as indicated by the mean total scores at the BMRQ greater than 40 for all subjects (76.6 ± 1.9).

3.2 Subjective responses to musical stimuli

Results from the arousal rating confirmed that Rossini and Stravinsky music were perceived as exciting and Satie and Minkus music were perceived as relaxing (Table 1 and 2).

Table 1. Comparisons of the physiological measures among silence, exciting music and relaxing music (Statistical Model 1). Values are expressed as means (standard deviation).

	<i>Silence</i>	<i>Exciting Music</i>	<i>Relaxing Music</i>	<i>p value</i>
<i>SAM</i>	–	5.3 (0.1)	1.9 (0.1)	–
<i>LF (Hz)</i>	2307.1 (473.6)	4325.1 (2897)	1465.3 (202.1)	0.485
<i>HF (Hz)</i>	2517.8 (801.9)	3146.1 (1618.4)	1894.4 (508)	0.645
<i>LF/HF (Hz)</i>	1.6 (0.3)	2.2 (0.5)	2.4 (0.9)	0.429
<i>HR (BPM)</i>	71.6 (1.9)	70.9 (2.1)	70.6 (2)	0.026
<i>SCL (μS)</i>	1.0 (0.3)	-1.2 (0.4)	-1.6 (0.5)	0.001
<i>SCR Amplitude (μS)</i>	1.0 (0.2)	0.6 (0.1)	0.8 (0.3)	0.448
<i>SCR Magnitude (μS)</i>	0.4 (0.1)	0.3 (0)	0.2 (0)	0.022
<i>MeanBTP (μm)</i>	3.0 (0.2)	2.6 (0.2)	2.4 (0.2)	0.003
<i>MaxBTP (μm)</i>	8.9 (3.8)	8.6 (3.5)	8.5 (3.2)	0.773

SAM: Self-Assessment Manikin; LF: Low Frequency; HF: High Frequency; HR: Heart Rate; SCL: Skin Conductance Level; SCR Amplitude: Amplitude of skin conductance responses; SCR Magnitude: Weighted amplitude of skin conductance responses; BTP: Brain Tissue Pulsatility.

Table 2. Comparisons of the physiological measures among silence and the 4 musical excerpts (Statistical Model 2). Values are expressed as mean (standard deviation).

	<i>Silence</i>	<i>Rossini</i>	<i>Stravinsky</i>	<i>Satie</i>	<i>Minkus</i>	<i>p-value</i>
<i>SAM</i>	–	5.5 (0.2)	5.2 (0.2)	1.6 (0.1)	2.2 (0.2)	–
<i>LF (Hz)</i>	2307.1 (473.6)	7277.7 (6078.8)	1354.2 (344.2)	1373.1 (183.5)	1560.6 (315.8)	0.462
<i>HF (Hz)</i>	2517.8 (801.9)	4193.3 (3226.9)	1632.1 (649.4)	1597.6 (436)	1848.9 (549.3)	0.592
<i>LF/HF (Hz)</i>	1.6 (0.3)	2.2 (0.6)	2.4 (0.7)	2.1 (0.5)	2.9 (1.4)	0.849
<i>HR (BPM)</i>	71.6 (1.9)	72.2 (2.2)	70.6 (2.1)	71.6 (1.9)	70.9 (2.2)	0.216
<i>SCL (μS)</i>	1.1 (0.3)	-1.9 (0.5)	-0.8 (0.4)	-1.7 (0.5)	-1.8 (0.7)	0.001
<i>SCR Amplitude (μS)</i>	1 (0.2)	0.6 (0.1)	0.5 (0.1)	0.6 (0.1)	0.9 (0.6)	0.722
<i>SCR Magnitude (μS)</i>	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)	0.2 (0.1)	0.2 (0.1)	0.083
<i>MeanBTP (μm)</i>	3 (0.2)	2.7 (0.2)	2.5 (0.2)	2.5 (0.3)	2.2 (0.2)	0.012
<i>MaxBTP (μm)</i>	8.9 (3.8)	8.4 (3.4)	8.8 (3.8)	8.9 (3.7)	8.1 (3.5)	0.398

SAM: Self-Assessment Manikin; LF: Low Frequency; HF: High Frequency; HR: Heart Rate; SCL: Skin Conductance Level; SCR Amplitude: Amplitude of skin conductance responses; SCR Magnitude: Weighted amplitude of skin conductance responses; BTP: Brain Tissue Pulsatility.

3.3 BTP reactivity to musical stimuli

In Model 1, which compared BTP among the 3 conditions of silence, exciting music and relaxing music, repeated-measure ANOVA reported a significant change in meanBTP among the 3 conditions [$F(2, 46) = 6.833$; $p=0.003$]. Pairwise comparisons showed that meanBTP was significantly decreased with relaxing music compared to silence ($p=0.003$, after Bonferroni correction; Cohen's $d=3.0$); (Figure 1a). No significant effect was found between exciting music and silence, nor between exciting and relaxing music.

In Model 2, which compared BTP among the 5 conditions of silence and the 4 musical excerpts, repeated-measures ANOVA showed a significant change in mean BTP among the 5 conditions [$F(4, 92) = 3.406$; $p= 0.012$]. Pairwise comparisons showed that BTP was significantly decreased with Minkus music compared to silence ($p=0.008$, after Bonferroni correction; Cohen's $d=4.0$); (Figure 1b, Figure 2 and supplementary material 1). A trend for significance was found between Minkus and Rossini music ($p=0.091$, after Bonferroni correction; Cohen's $d=2.5$). No significant

effect was found between the other music excerpts and silence, nor among the different music excerpts. No significant difference was found in MaxBTP values for both models.

Figure 1. 1a: Line charts of the significant comparisons of BTP and peripheral measures among silence, exciting music and relaxing music (Model 1). **1b:** Line charts of the significant comparisons of BTP and peripheral measures among silence and the 4 musical excerpts (Model 2). Means and standard deviations are shown in the graphs.

Figure 1a.

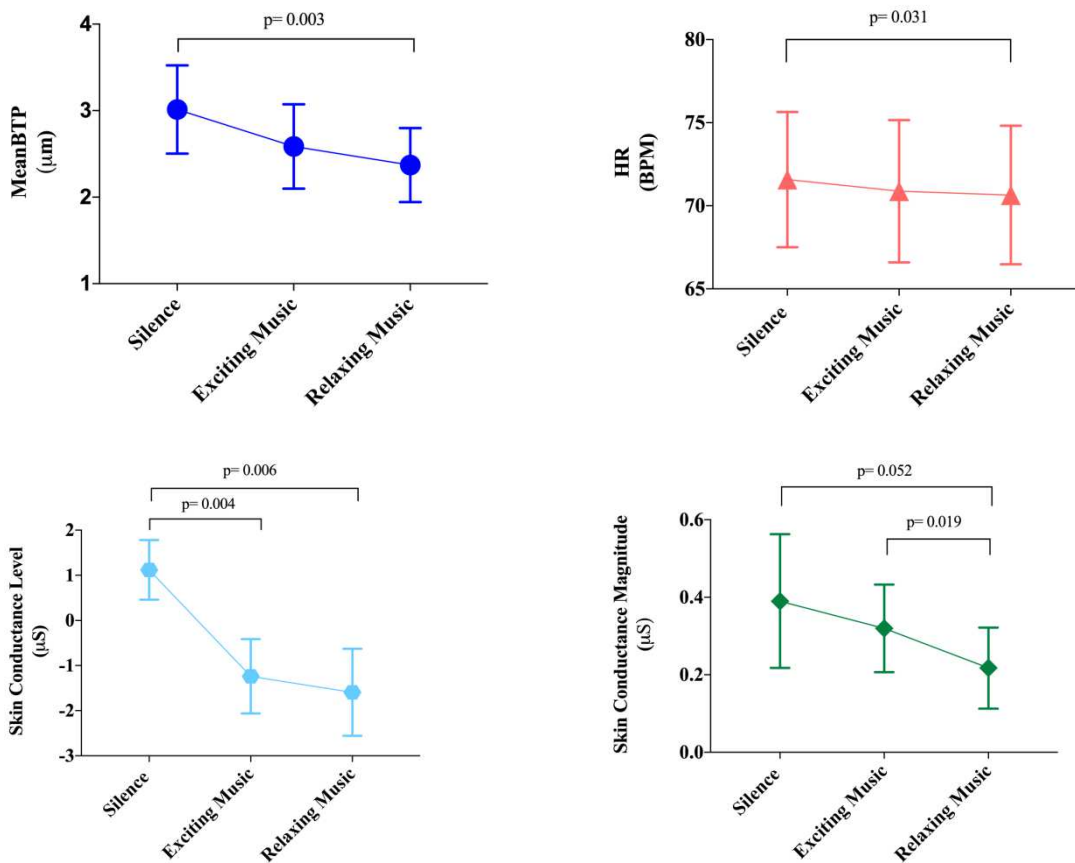


Figure 1b.

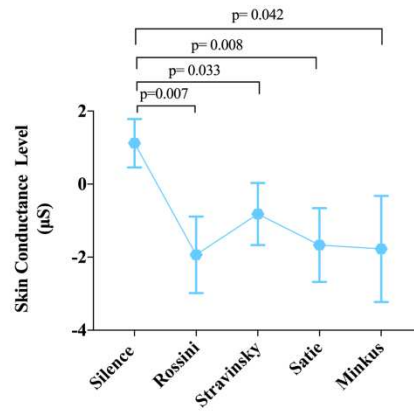
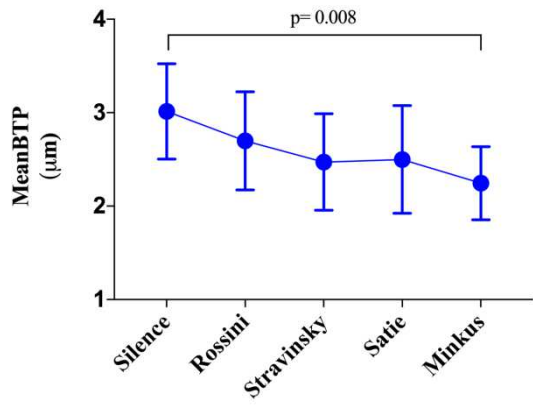
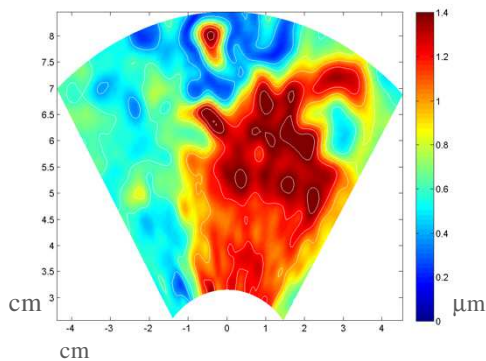
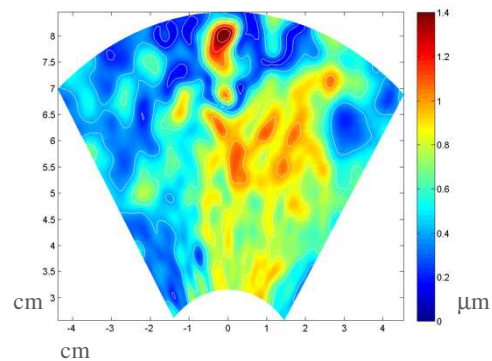


Figure 2. Brain Tissue Pulsatility (BTP) color maps from a representative subject during the different phases of the experimental design. We applied the Horn—Schunck method to estimate the optical flow and displacement speed of each volume in the region of acquisition, the color maps of which show maximum values. Consistent with our general results, subject shows high BTP amplitudes during silence (**2a**), and low BTP amplitudes during Minkus music (**2b**). A video clip of

2a.



2b.



these results is also provided as a supplementary material in the online version.

3.4 Peripheral physiological responses to musical stimuli

3.4.1 Heart Rate and Heart Rate Variability. HR was significantly different among the 3 conditions [$F(2, 46) = 3.960$; $p = 0.026$]. Pairwise comparisons showed that heart rate was significantly lower with relaxing music compared to silence ($p = 0.031$, after Bonferroni correction; Cohen's $d = 0.5$). No significant effect was found between exciting music and silence, nor between exciting and relaxing music; (Figure 1a). We found no significant difference in HRV values for both models.

3.4.2 Skin Conductance. SCR magnitude and SCL were significantly different among the 3 conditions [$F(2, 46) = 5.202$; $p = 0.022$ et $F(2, 46) = 10.742$; $p = 0.001$, respectively] (Figure 1a). Pairwise comparisons showed that SCL decreased with both relaxing and exciting music compared to silence ($p = 0.004$, after Bonferroni correction; Cohen's $d = 6.2$ and $p = 0.006$, after Bonferroni correction; Cohen's $d = 6.3$, respectively). SCL was significantly different among the 5 conditions [$F(4, 84) = 7.183$; $p = 0.001$] (Figure 1b). No significant difference was found in SCR amplitude for both models.

4. DISCUSSION

The principal finding of our study was that the amplitude of the brain pulsatile movements, as assessed by meanBTP, decreased with relaxing music compared to silence. More specifically, because meanBTP corresponds to the averaged value of thousands of brain volume pulsations and because we found no significant change in MaxBTP, which informs on only the largest pulsatility due to the middle cerebral artery, our results suggest that relaxing music elicits a general decrease in brain pulsatility, without significant changes in large-artery pulsatility.

Change in Cerebral Blood Flow (CBF) is the most plausible explanation to account for the decrease in meanBTP with relaxing music. Indeed, a decrease in CBF is thought to lower intracranial pressure and to lower the amplitude of the brain tissue pulsatile movements (Kucewicz *et al.*, 2008). Our results are therefore consistent with previous studies that found a decrease in CBF with a slow-pace music compared to a fast-pace music (Trappe, 2010; Bernardi *et al.*, 2009, 2006). However, these studies used TCD to investigate CBF in large arteries and our result suggest that decrease in CBF with relaxing music may be more sensitively occurring in small cerebral arteries whereas the largest artery investigated in our study, namely the middle cerebral artery, may not exhibit lowering in CBF with relaxing music.

Because TPI primarily measures movements of the brain parenchyma which only indirectly relate to CBF, other factors may be involved in our results, including changes in elasticity of the brain tissue itself. Indeed, BTP was found to vary as a function of the brain tissue composition that affects elasticity (Ternifi *et al.*, 2014). Moreover, not only chronic but also rapid change in the elasticity of the brain tissue could occur with various external stimulations, over a time scale from seconds to minutes (Parker, 2017). These changes not solely involve vascular dilation and contraction but also mechanisms such as intracellular pressure, which is mainly related to tissue properties. Stimulation of contractile machinery of cells may induce local internal stress in the elastic matrix, thus resulting in changes in the viscoelastic properties of the tissue (Parker, 2017). Finally, it has been suggested that synaptic activity and some cerebral mechanical properties shared reciprocal relationships. Indeed, changes in neuronal activity are followed by changes in arteries pulsatility that cause variations in local cerebral blood flow and metabolism, while in turn, changes in arteries pulsatility modulate structural and functional properties of neuronal activity, such that arterial pulsatility modulate synaptic densities near the blood vessel walls, notably (Urrecha *et al.*, 2017). Therefore, not only changes in CBF but also in synaptic activity may account for the changes in BTP observed with relaxing music, such as a lowering in BTP may involve a lowering in synaptic activity.

We found that markers of the Autonomous Nervous System (ANS), namely HR and SC, also decreased with relaxing music compared to silence, consistent with BTP results. This may suggest that ANS activity influences changes in BTP during music listening. Interestingly, consistent findings suggest that ANS activity contributes to changes in the fMRI signal (Özbay *et al.*, 2019). However, compared to HR and SC, which principal determinant is ANS reactivity, BTP has multiple determinants that may involve not only ANS activity but also CBF reactivity and related mechanisms (Kucewicz 2007, 2008), Blood Pressure (Biogeu et al., 2016), Neural activity (Angel et al., 2018) and brain parenchyma structure (Desmidt et al., 2017; Ternifi et al., 2014). Moreover, BTP directly relates to the physiology of the brain, whereas HR and SC are markers of the peripheral physiology. In addition, HR is a physiological marker of temporal changes, whereas BTP informs on spatial changes in the brain physiology (changes in amplitudes of brain movements) and the two measures may not be directly related but may have a factor in common, most probably ANS activity. Finally, we cannot exclude that our findings indicate a general effect of relaxing music on ANS which has an impact not only on peripheral measures (HR and SC) but also on central measures (BTP), and the relaxing effect of music on the brain could be mediated by the ANS.

We found that ‘the entrance of the shades’ by Minkus showed the most significant effect on the physiological parameters. Previous literature has suggested that musical tempo is a major determinant of physiological changes in music perception, with a slow tempo inducing a decrease in heart rate, respiratory rate, skin conductance, blood pressure (Koelsch & Jäncke, 2015) and cerebral blood flow (Bernardi *et al.*, 2006) compared to a fast tempo. Because only Minkus music and not Satie music, which both have a slow tempo, had a significant effect on physiological measures, our results suggest that some features other than tempo pace may have a role in physiological reactivity to music. Minkus excerpt is primarily distinct from Satie excerpt because of a ternary tempo for the first one and binary for the latter. The ternary (6/8) and constant tempo provokes a rocking effect; the musical excerpt is characterized by a same theme which repeats itself continuously; tone is Major, with a unique modulation in minor tone during the central phase. The repetition of the same, calm, dancing, slow and reassuring musical pattern may induce a perception of recognition which may result in a calming and relaxing effect. These effects may explain the decrease in physiological measures observed during Minkus but not Satie music.

Literature generally reports that HR and SC increase with an exciting music and decrease with a relaxing music (Koelsch & Jäncke, 2015). In our study, only the magnitude of SCR was significantly lower with relaxing music compared to exciting music. Interestingly, we investigated not only differences between exciting and relaxing music but also between silence, exciting and relaxing music. Literature reports inconsistent results of the effects of music compared to silence on

physiological measures, with studies showing small changes in HR and HRV with music, which are often statistically not significant, varying during presentation and not consistent across studies (Koelsch & Jäncke, 2015). In our study, the most consistent effect was observed with the difference between silence and relaxing music and this result may be related to the original design of our protocol. Indeed, in most of the music perception protocols, silence periods consist on no other task than no presentation of music, whereas in our study, we decided to include a visual perception concurrent task throughout the protocol, so as to control for attention. Thus, we cannot exclude that greater BTP during silence period is related to an increase attentional allocation to visual stimuli, as visual perception and greater cognitive activity were found to increase BTP (Angel *et al.*, 2018; Kucewicz *et al.*, 2007). Nevertheless, BTP usually increases only with intense visual stimuli and it is unlikely that neutral images from the OASIS bank significantly influenced BTP. Moreover, the visual presentation was similar during the whole task and the observed differences are more likely due to the presentation of music excerpts with obviously differed between silence periods and music presentation. It can also be hypothesized that silence may increase stress levels in the experimental context of laboratory in young adults who are not used to experiment silence in daily life.

We did not find any significant difference in heart rate variability measures (HRV) between silence and music. In the similar previous study from Iwanaga (Iwanaga *et al.*, 2005), there was no significant different difference in HRV between music and silence at the first presentation of the stimuli, whereas a significant difference appeared when the task was repeated a second time at a different moment of the day. The author concluded that HRV changes may reflect habituation to music perception. We did not test habituation in our study and our results regarding HRV are consistent with Iwanaga study, even for the two other music excerpts that were not including in Iwanaga study. In general, there has been a debate on whether HRV constitutes a reliable marker for physiological response to music (Koelsch & Jäncke, 2015) and our result suggest that HRV may not be sensitive enough compared to BTP, HR and SC.

Our study has limitations, including the fact that BTP measures were not strictly synchronized with the onset of musical stimuli via the e-prime software which connection was not available with the Ultrasound Antares Scanner. In addition, we did not proceed to a systematic analysis of the acoustic characteristics of the studied musical excerpts, which limits the interpretation of their specific effects. Moreover, for an optimal control of the effect of musical excerpts on physiological changes, future experiments could benefit from non-musical or noise control stimuli, and a loudness change task to control attention. In addition, a recent experiment identified emotional domains of musical excerpts (Shen *et al.*, 2018), and future studies may include the emotional characteristics of musical

excerpts to further investigate the differential effects of various emotion types on physiological changes during music listening. In conclusion, our study suggests that TPI may constitute a marker of cerebral biomechanical reactivity to musical perception, which may involve changes in amplitudes of pulsatile brain movements. Our results have various implications, notably the potential of using TPI to characterize the brain physiology related to music perception in various experiments in healthy volunteers, as well as using TPI as a non-invasive, low-cost and easy-to-implement biomarker of physiological response to music in clinical populations. Interestingly, a recent TPI study showed that individuals with major depression exhibit a baseline increase in BTP (Desmidt *et al.*, 2017). Because music therapy constitutes a potential treatment option in depressive disorders (Erkkilä *et al.*, 2011) and because we found that classical music with certain relaxing characteristics decreases BTP, we may suggest that TPI could be used as a biomarker for treatment response in individuals with depression involved in music therapy trials. Moreover, this may lead to a deeper understanding of brain modulation with music therapy for depression, which is focused so far on EEG-measure (Fachner, Gold & Erkkilä, 2012). Besides, we may suggest that relaxing music with characteristics such as the ‘Entrance of the shades’ by Minkus could be particularly relevant in music therapy trials 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 (Wählin *et al.*, 2014; O’Rourke & Hashimoto, 2007) and to account for the greater risk of stroke and small vessels disease in individuals with depression (Desmidt *et al.*, 2017).

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SUPPLEMENTARY MATERIAL

Video clip of Brain Tissue Pulsatility (BTP) color maps from a representative participant during silence (first 10 seconds), then Minkus' "Entrance of the shades" (subsequent 35 seconds) and finally silence again (final 5 seconds). Consistent with our general results, BTP decreases during Minkus excerpt compared to silence.