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Profound Haemodynamic Response in the Prefrontal cortex Induced by Musical Stimuli

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Abstract

Blood-oxygen dynamics in response to prefrontal cortex (PFC) activity are important for emotional responses to sensory stimuli, such as music. However, the local neuronal circuits involved in the encoding of musical information by the PFC remain unknown. We aimed to examine alterations in prefrontal activity patterns while participants listened to musical pieces with different properties. Brain function was examined in 28 participants (14 men, 14 women) while they listened to two musical pieces ("Salut d'Amour" and "Pomp and Circumstance Marches") using functional near-infrared spectroscopy (fNIRS), electrocardiography, and pulse oximetry. The delta oxyhemoglobin (ΔOxy-Hb) levels were significantly reduced in the left lateral PFC during "Pomp and Circumstance Marches", relative to those observed during "Salut d'Amour". Wavelet analyses of brain metabolism revealed that "Salut d'Amour" altered brain activity between 0.015-0.030 Hz, whereas "Pomp and Circumstance Marches" sparsely activated the brain at 0.015 Hz and activated the dorsolateral and orbitofrontal PFC at 0.030 Hz. These findings demonstrate that different musical stimuli exert differential effects on brain metabolism associated with neural activity in the PFC. These patterns may shed light on the mechanisms underlying music processing in the brain, and the overall role of music in promoting mental health and creation of better circumstances for physiological conditions in human.

Keywords: Music; Near infra-red spectroscopy; Prefrontal cortex; Oxyhemoglobin

Abbreviations: PFC: Prefrontal Cortex; fNIRS: Functional Near-Infrared Spectroscopy; ΔOxy-Hb: Delta Oxyhaemoglobin; SPECT: Single-Photon Emission Computed Tomography; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; Δdeoxy-Hb: Delta Deoxyhaemoglobin; ΔTotal-Hb: Delta Total Haemoglobin; LF/HF: Low Frequency/High Frequency

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Introduction

Research has indicated that humans listen to music primarily to regulate arousal and mood, express social connections, and achieve self-awareness [1]. Generally, music can be described based on the following components: (1) pitch, which governs melody and harmony; (2) rhythm; and (3) timbre. Previous studies have demonstrated that music affects brain activity related to emotion [2-7]. Anatomical and physiological comparisons of healthy individuals and those with amusia have led to the development of a hypothetical model for information processing during music listening, which proposes the following: (1) Sound processing occurs between the cochlea and primary auditory cortex; (2) pitch recognition for melody, rhythm, and timbre occurs in the auditory cortex; (3) emotional processing occurs in the insula and limbic area; (4) working memory for rhythm occurs in the parietal lobe; and (5) integrative informational processing for harmony, emotion, working memory, and behavioral output occur in the prefrontal cortex (PFC) [8-10]. The results of functional imaging (e.g., single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI)) studies have indicated that the prefrontal and cingulate cortices, auditory cortex, and thalamus are active during music listening-further supporting this model [11-13]. Additional studies have revealed that participants perceive pitch *via* the frontal and temporal lobes during music listening [14]. Although the accumulated evidence indicates that music induces various affective states and processes associated with emotion, memory, and cognition [15,16] the mechanisms underlying the individual neural events in the PFC remain to be determined.

Functional near-infrared spectroscopy (fNIRS) is a powerful tool for visualising brain activity in a non-invasive manner [17] due to the variety of possible experimental set-ups and its high temporal resolution (on the order of seconds) [18]. In fNIRS, the time-dependent dynamics of oxyhaemoglobin (ΔOxy-Hb), deoxyhaemoglobin (Δdeoxy-Hb), and total haemoglobin (ΔTotal-Hb) in the prefrontal region can be calculated based on near-infrared light absorbance at 770 nm and 840 nm, according to the modified Lambert-Beer Law [19]. Conventional analyses have demonstrated that the recorded data include both functional brain activity and signal noise associated with skin blood flow, heart rate variability, and body movement. Thus, it is difficult to isolate signals originating from brain activity only. However, a valid method for extracting functional components from total fNIRS data has recently been developed (i.e., the haemodynamic modality separation method) [20]. Yamada et al. [20] developed the haemodynamic modality separation method be examining various spatial placements of NIRS illuminators and detectors in the presence or absence of independent signals of brain activity (e.g., skin blood flow). The parameters critically separate the NIRS data into brain-dependent and brain-independent components, enabling one to isolate brain activity using NIRS.

In summary, ΔOxy-Hb is well correlated with brain activity [20-22] suppression of ΔOxy-Hb occurs during pleasant feelings or relaxation [23,24]. As fNIRs poses less of a burden to participants relative to other functional assessments (e.g., functional MRI, PET, etc.), this method is particularly advantageous for determining prefrontal brain activity associated with psychological states following the presentation of musical stimuli because recording can be conducted in near-natural settings.

In the present study, we aimed to examine alterations in prefrontal activity patterns while participants listened to musical pieces with different properties, in order to more fully elucidate the neural mechanisms underlying PFC activity during music listening.

Methods

Participants and ethical considerations

Twenty-eight healthy Japanese participants (men: 14; women: 14; age range: 29-47 years old) participated in the present study. Left-handed participants and those with a musical background were excluded from the analysis. Informed consent was obtained from all participants prior to the onset of experiments. We conducted fNIRS recording, pulse oximetry, and electrocardiogram tests as described below. Until the onset of all experiments, the participants were instructed to keep their eyes closed, and to remain calm and relaxed. All experimental procedures were in accordance with the Declaration of Helsinki and were approved by the ethical committee of Kyoto University in Japan prior to the onset of the experiments.

Characteristics and control of musical stimuli

Two musical pieces composed by Edward Elgar (AC 1857-1934), titled “Salut d’Amour” and “Pomp and Circumstance Marches”, were used to induce neuronal activity during recordings. The sound intensity of the music was measured using a DT-85 sound-level meter (MK Scientific Inc., Kanagawa, Japan). Musical scale **(Figure 1a)** was analysed using Wave tone (open-source software, Japan. Link: http://ackiesound.ifdef.jp/doc/wthelp_eng/index.html). The power spectra **(Figures 1b and 1c)** were analysed using the open-source software program Audacity (Boston, MA, USA). The musical stimuli tasks **(Figure 1)** were programmed using the Spstim2 system (Access Vision, Co. LTD, Kanagawa, Japan). Spstim2 triggered the music stimuli for each participant and simultaneously controlled the external trigger signals of the fNIRS equipment (Spectratech OEG-16, Spectratech, Tokyo, Japan; **Figure 2**).

fNIRS

The OEG-16 system was used to record fNIRS data. The 16-ch illuminator and detector (time-division multiple access method) of the fNIRS instrument were tightly attached to the surface of the scalp. The placement of the illuminators and detectors was calculated between participants, and fixed forehead skin positions were marked with a seal and matched to the standard 10-20 cranial positions [25] for the prefrontal region. Measurement began following confirmation that all illuminator and detector signals were being transmitted appropriately against the background noise. To reduce motion artefacts during recording, participants were asked to sit in a chair and remain calm with their eyes closed for 10 min, until the onset of the experiment. Participants then listened to the music through the computer using ear buds. The resting state time and the start of the music were controlled by Spstim2 software (Spectratech, Tokyo, Japan). Following a resting state of 1 min, fNIRS data were recorded during music listening, followed by another resting state of 1 min. All fNIRS traces were normalised by dividing the data by the average values of resting state. A moving average was calculated to reduce noise.

Heart rate variability was measured *via* pulse oximetry and electrocardiography, as described in the following section. We used the haemodynamic modality separation method [20] to isolate brain fNIRS data from the raw data. Statistical analysis was conducted among all participants, and ΔOxy-Hb, Δdeoxy-Hb, and ΔTotal-Hb traces were obtained from the average of the data from all participants (n=28).

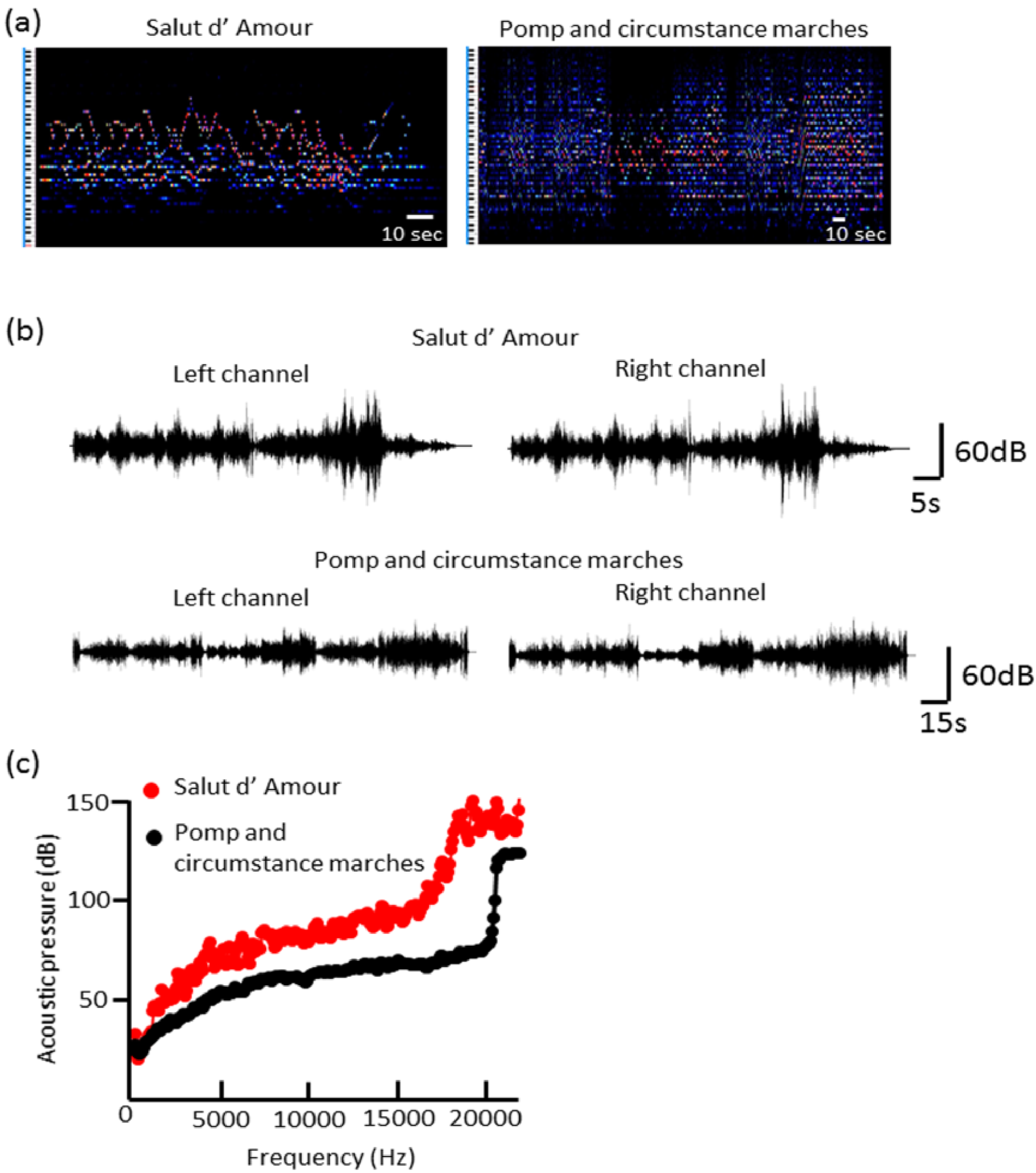

Figure 1 **Sound properties of the musical pieces.**

(a) Time course of the music scale. Vertical axis: Keyboard based on the music scale. Horizontal axis: Time course. Bar: 10 s.

(b) Music waveform. Participants were exposed to two musical pieces at the same levels of sound intensity.

(c) Fourier transformation of the musical spectrum.

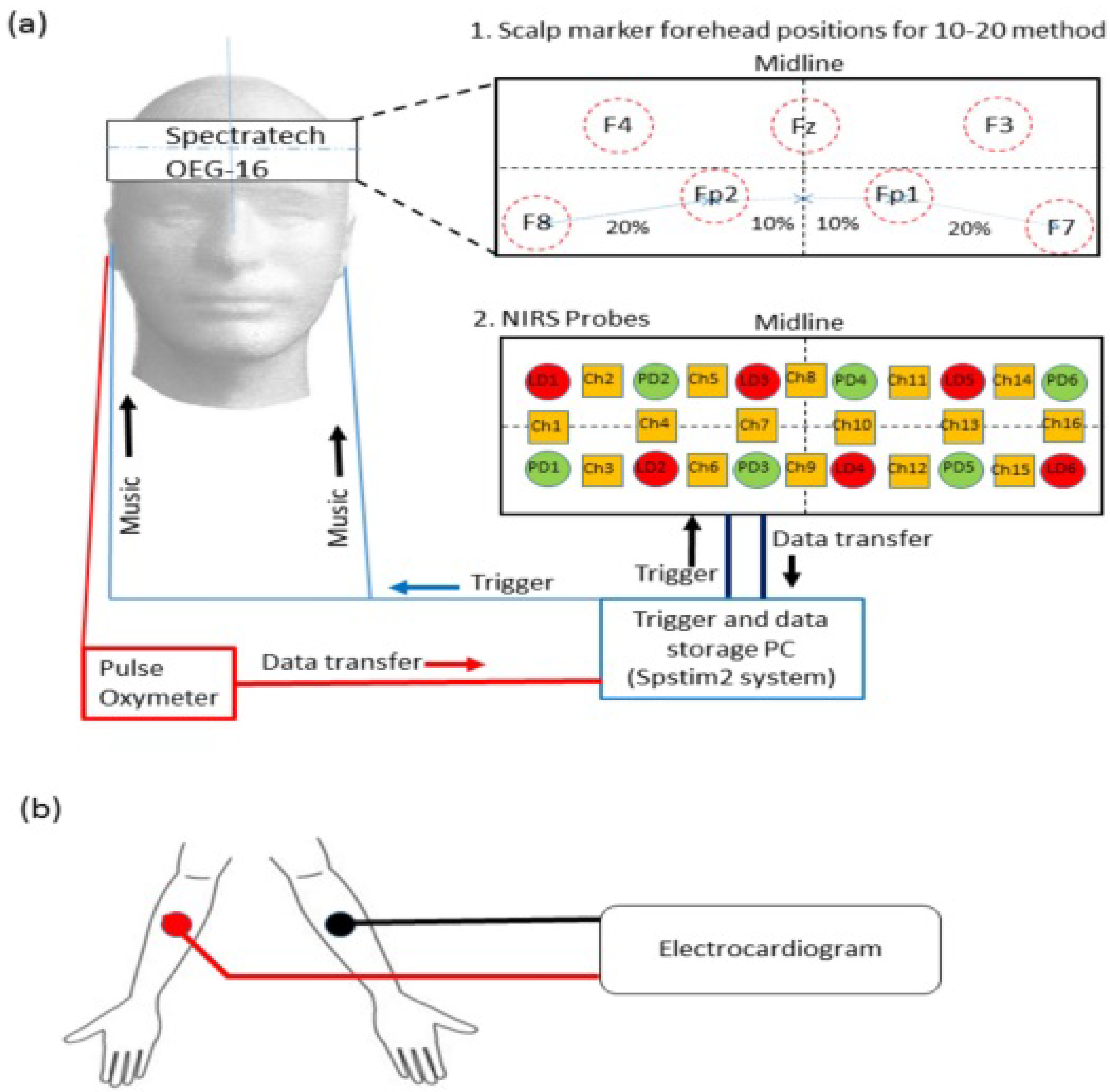

Figure 2 **Functional near infra-red spectroscopy (fNIRS) setting and experimental procedures.**
Participants underwent simultaneous recording of fNIRS, pulse oximetry, and electrocardiogram (ECG) data.

(a) Left panel: A participant wearing the OEG-16 system (fNIRS apparatus) on the forehead, with emitter-detector pairs based on the 10-20 system (i.e., right panel: 1) [25]. A face was drawn by Yuki Murakami (co-author). 2. fNIRS probes. LD: Emission; PD: Detection; Ch: Measurement of ΔHb. The Spstim2 program triggered the onset of music and stored time course data.

(b) Setting of electrocardiogram recordings.

Pulse oximetry

Cutaneous blood flow, blood oxygen saturation (SpO2) levels, and heart rate were recorded using a pulse oximeter (Oxytrue, BluePoint Medical, Selmsdorf, Germany). Recording devices were attached to the participants' ear buds. Pulse rate and fNIRS measurements were obtained simultaneously. SpO2 data recorded during the tasks were stored and analysed using Oxytrue A PC software (BluePoint Medical, Selmsdorf, Germany). These procedures were performed in accordance with manufacturer guidelines.

Electrocardiography

Electrocardiograms (ECG) were recorded using handheld ECG

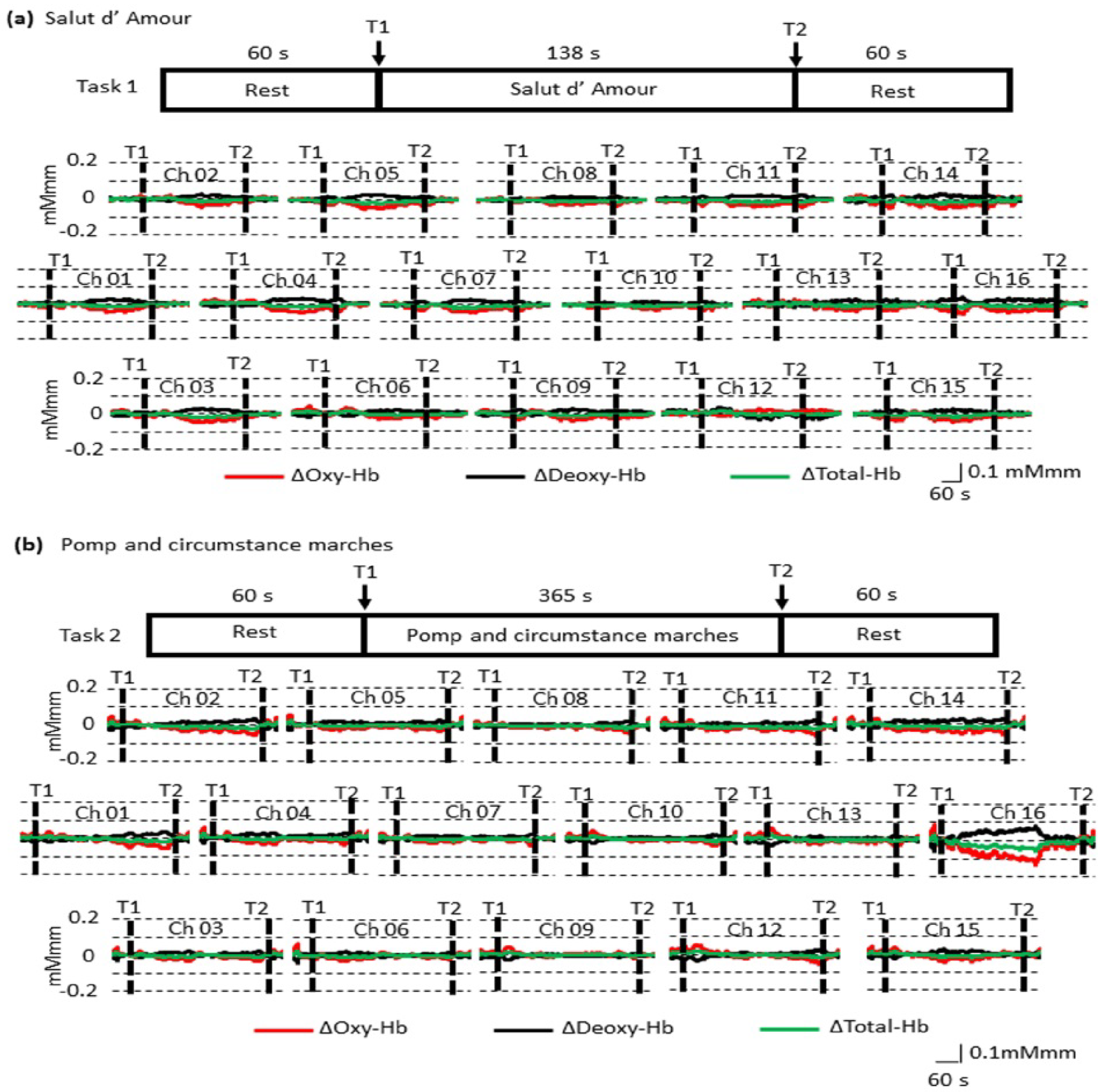

Figure 3 **Changes (Δ) in Hb dynamics according to musical stimuli.**

Participants listened to music between Rest 1 and Rest 2. T1: onset of music; T2: completion of music. Red traces: ΔOxy-Hb; black traces: ΔDeoxy-Hb; green traces: ΔTotal-Hb.

a) "Salut d'Amour".

b) "Pomp and Circumstance Marches".

instruments (CheckMyHeart, Trytech Co. LTD, Tokyo, Japan). Two ECG electrodes were individually attached to the right and left forearms of each participant. Participants were encouraged to remain calm during recordings. Heart rate variability at rest and during music listening were applied to the power spectrum (i.e., low frequency (LF), high frequency (HF), and LF/HF) analyses to determine autonomic nervous system activity using Check My Heart software (Daily Care Biomedical Inc., Taiwan).

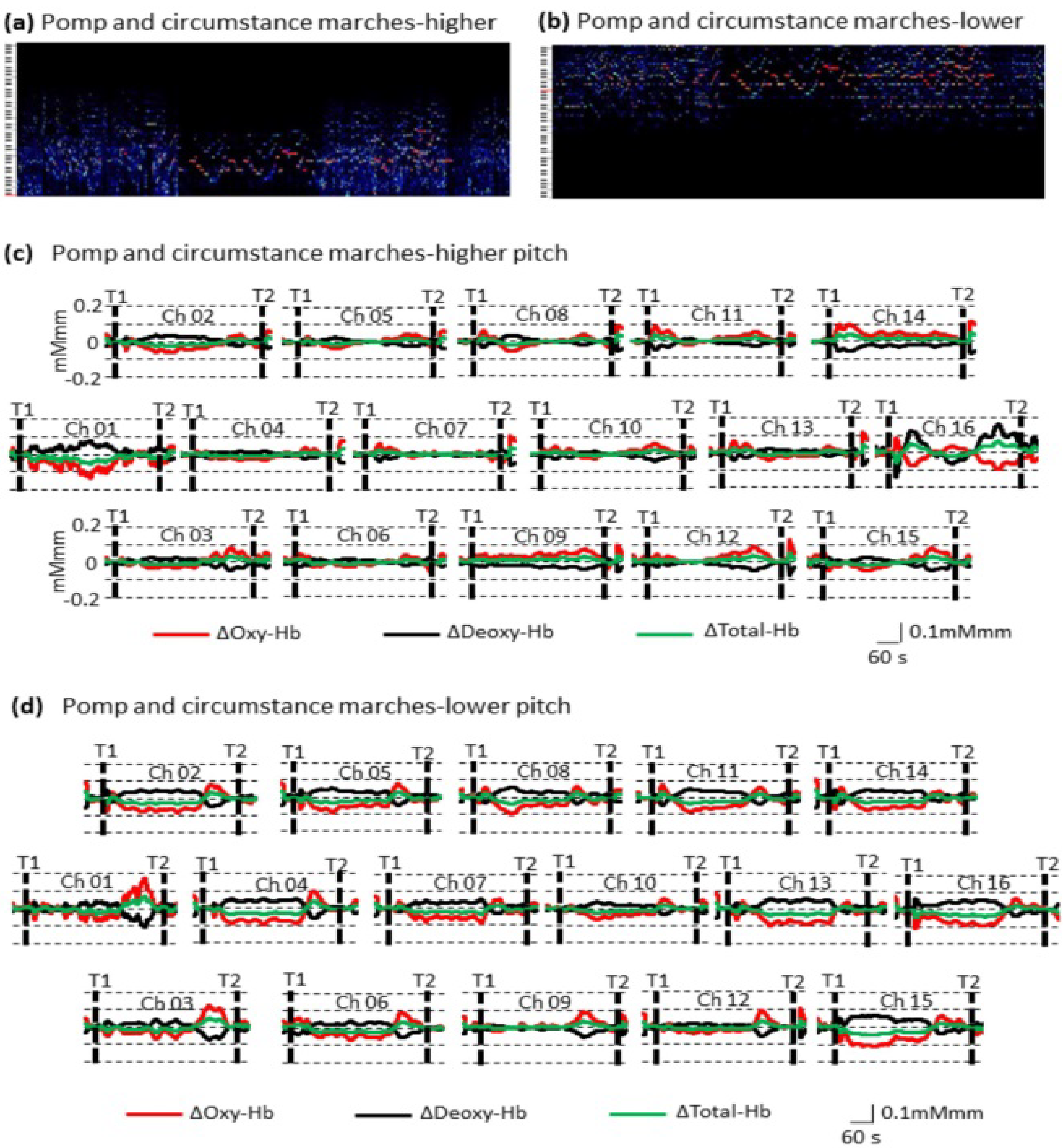

Figure 4 **Pomp and circumstance marches changing pitch.**

Pitch of pomp and circumstance marches was changed to higher pitch (a) and lower pitch (b). Participants listened to music between Rest 1 and Rest 2. T1: Onset of music; T2: Completion of music. Red traces: ΔOxy-Hb; black traces: ΔDeoxy-Hb; green traces: ΔTotal-Hb.

Statistical analyses

Analyses of fNIRS data were performed using Brain Suite software (BR systems Inc. Kanagawa, Japan), while Graph Pad Prism (Graph Pad Software Inc, CA, USA) was used to identify statistically significant differences. We analysed average ΔOxy-Hb traces

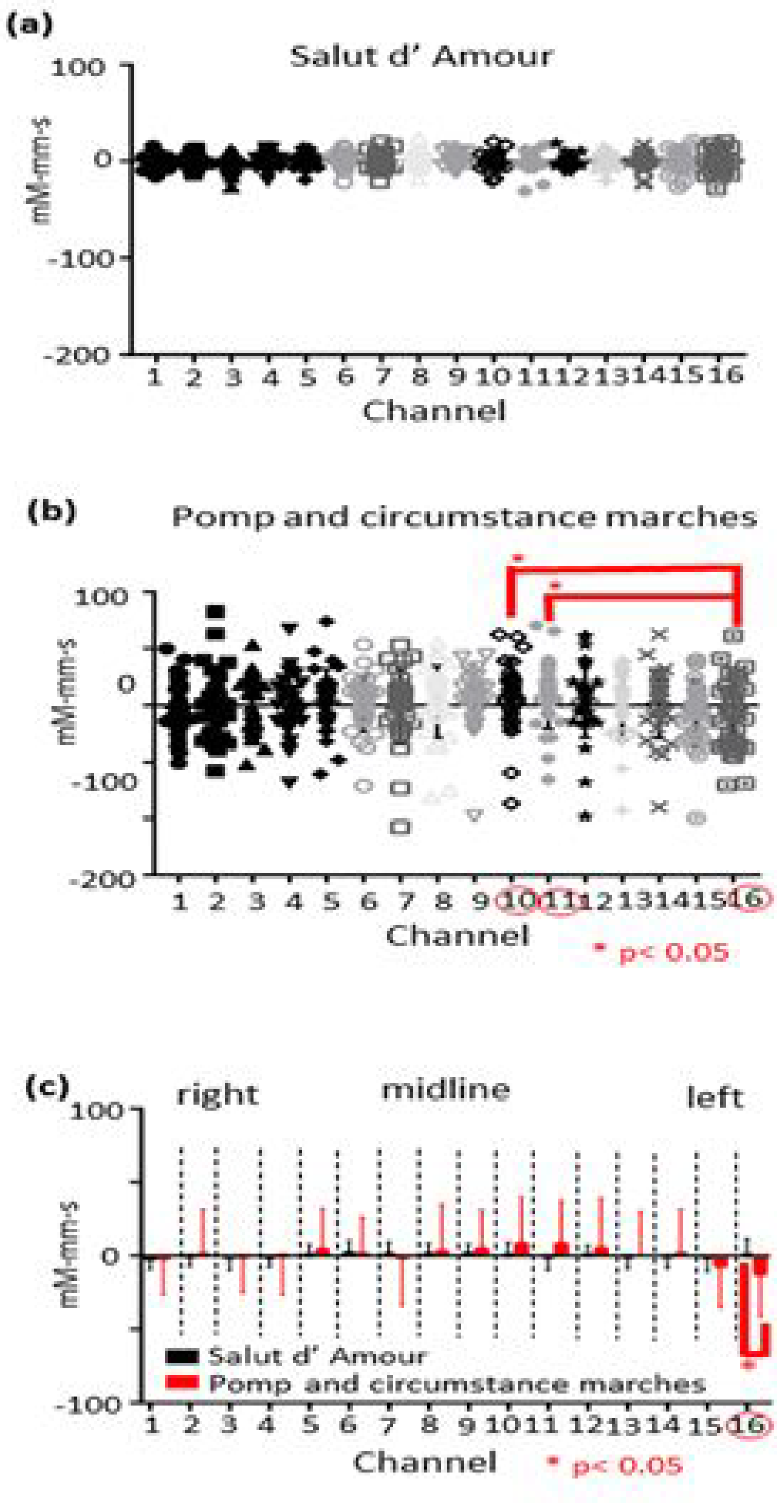

Figure 5 **Significant alterations in ∆Oxy-Hb integral values were observed when participants listened to "Pomp and Circumstance Marches".** The integral ∆Oxy-Hb values for each participant during music listening.

a) "Salut d'Amour".
b) "Pomp and Circumstance Marches".
c) Summary of the data for each participant. Comparison among channels was performed for both (a) and (b). Dashed lines indicate that comparisons were performed between the two pieces of music, rather than between two channels (c). Statistical comparisons were performed using Tukey's tests [(a) and (b)] and paired t-tests (c). *statistically significant difference at $p<0.05$.

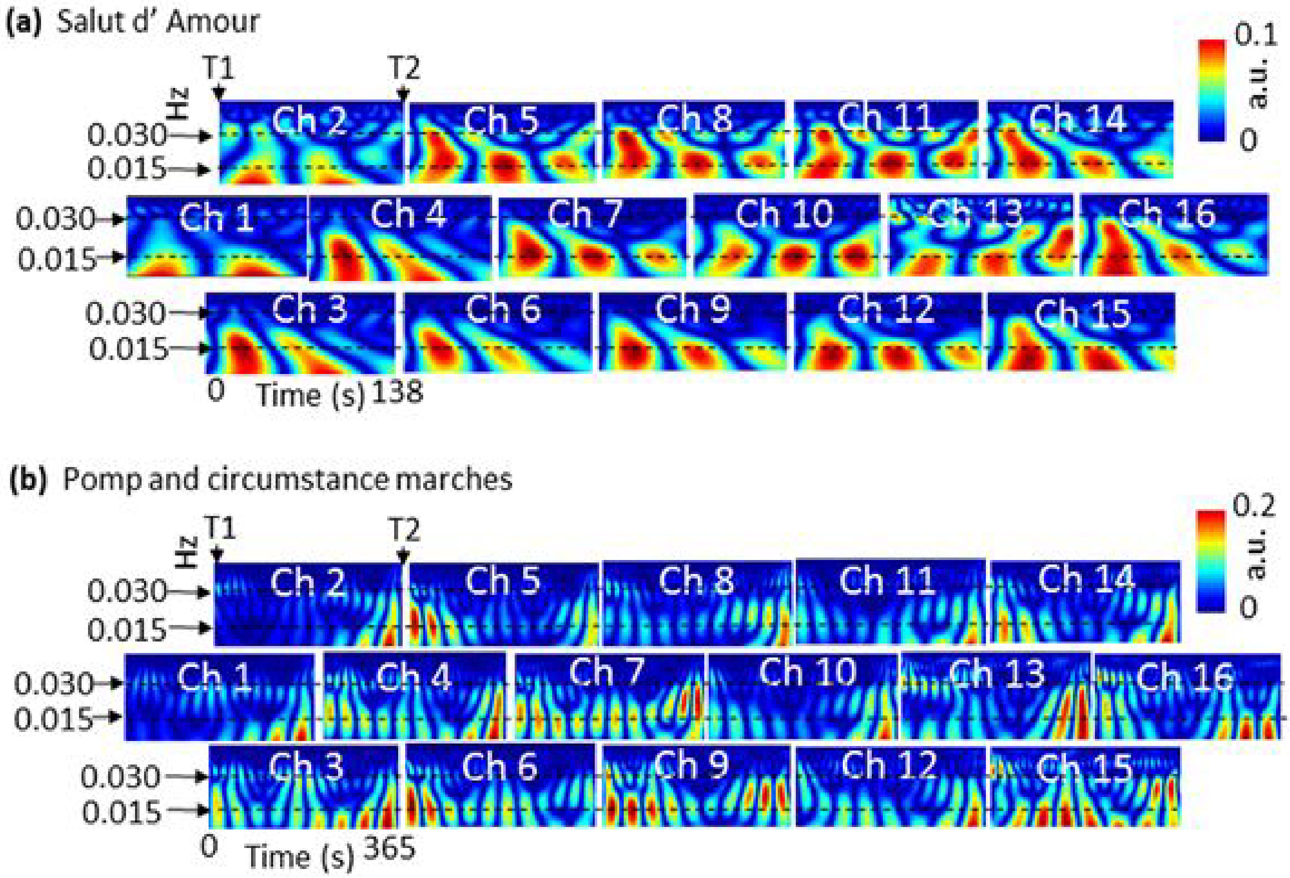

Figure 6 **Wavelet transformation.**

a) "Salut d'Amour".

b) "Pomp and Circumstance Marches". The Morlet wavelet was used as the window function. Vertical axis: Frequency; horizontal axis: Time (s) after music onset; T1: start of the music; T2: cessation of music. Dashed lines: oscillation at 0.015 Hz (lower) or 0.030 Hz (upper).

Table 1 Instrumental characteristics of musical pieces.

Salut d'Amour		Pomp and Circumstance Marches	
String	**Sound Range**	**Woodwind**	**Sound Range**
Harp	Cb-1-Gb6	Piccolo	C4-C7
		Flute	C3-C6
		Oboe	D5-C5
		Clarinet	D5-Bb5
		Bass Clarinet	D5-Bb2
		Bassoon	Bb0-Bb3
		Double Bassoon	C-1-Eb0
		Brass	
		Horn	F1-F4
		Trumpet	E2-F5
		Cornet	E2-F5
		Trombone	E1-B3
		Tuba	D0-Bb2
		Strings	
		Harp	Cb-1-Gb6
		Violin	G2-E6

		Viola	C2-C5
		Violoncello	C1-G4
		Contrabass	E0-C3
		Keyboard	
		Organ	C2-C7
		Percussion	
		Timpani	E1-A2
		Glockenspiel	G4-C7
		Snare Drum	-
		Bass Drum	-
		Cymbals	-
		Triangle	-
		Sleigh Bells	-

and integral values during music listening for each participant. We also performed a wavelet analysis of the averaged data using the Morlet wavelet (i.e., Gaussian window) for the human perception of music transcription [26]. Statistical differences in individual integral values among channels in the fNIRS detectors (i.e., different brain regions) were examined using Tukey's tests [27] and paired t-tests. Differences with p values less than 0.05 were deemed statistically significant.

Results

Characterisation of the musical pieces

We first analysed the sound properties of each musical piece. "Salut d'Amour" was played with the harp only, whereas the "Pomp and Circumstance Marches" were played with 25 instruments **(Table 1).** To evaluate the tone of the music, we analysed the musical scale against the time course of each piece using WaveTone software **(Figure 1a)**. Relative to "Salut d'Amour", the "Pomp and Circumstance Marches" were characterised by a wider range of musical tones. To avoid stimulation artefacts associated with auditory intensity, these musical pieces were played at similar sound intensities: 60 dB **(Figure 1b).** The results of these sound analyses were examined to determine the correlation between sound intensity and music frequency. The sound source in "Salut d'Amour" (red circles) exhibited a lower sound frequency than that in the "Pomp and Circumstance Marches" (black circles) at the same pitch level **(Figure 1c)**. These results suggest that "Pomp and Circumstance Marches" contained a greater number of musical tones than "Salut d'Amour".

Prefrontal oxy-haemoglobin dynamics during music listening

We recorded fNIRS data to investigate whether prefrontal activity is affected during music listening **(Figure 2).** Levels of ΔOxy-Hb-particularly those associated with channels (Ch) 16-were remarkably reduced relative to resting state values **(Figure 3a)** when participants listened to "Pomp and Circumstance Marches". Although increases in Δdeoxy-Hb were also observed, ΔTotal-Hb remained unaltered. Conversely, no significant alterations in Hb traces were observed when participants listened to "Salut d'Amour **(Figure 3b)".** We further examined whether pitch alone, rather than tone, altered brain activity when participants listened to "Pomp and Circumstance Marches". Two pitch alterations were performed; however, there was no remarkable difference in ΔOxy-Hb among the pitch variations **(Figure 4)**. These findings suggest that "Pomp and Circumstance Marches" predominantly altered brain activity in the dorsolateral region of left hemisphere.

Tukey's tests were used to compare data derived from each channel between the two musical pieces **(Figure 5).** Although no significant differences were observed for "Salut d'Amour" **(Figure 5a),** significant differences in ΔOxy-Hb values were observed for "Pomp and Circumstance Marches": Midline channels (Ch 5,6,8,9-11) exhibited positive values, whereas those in the left hemisphere (Ch 15 and 16) exhibited remarkable negative values **(Figures 5b and 5c**, red bars). Lower values were also observed in several other channels: Ch 1-4 7,14. Significant differences between Ch 16 and two other channels were observed: Ch 10 ($p=0.032$) and Ch 11 ($p=0.031$). These results suggest that "Pomp and Circumstance Marches" produced significant alterations in left PFC activity.

Differences in PFC activity induced by the two musical pieces

Previous studies have reported that the "Mozart effect"-which refers to the phenomenon in which music with a higher frequency and more fluctuations improves dopaminergic synaptic transmission and cerebral auto regulation [28] enhances memory function [29] and leads to better prognosis in children with epilepsy [30]. We therefore performed a wavelet analysis to determine whether our musical tasks induced different patterns of brain metabolism associated with neuronal firing **(Figure 6).** In wavelet analyses, increases in spectrum amplitudes are indicative of task-related neuronal firing [31]. Our findings demonstrated that "Salut d'Amour" result in broad brain activation at 0.015 Hz in every channel for the PFC **(Figure 6a)**. However, for the "Pomp and Circumstance Marches", robust neuronal firing was observed at both 0.015 Hz and 0.030 Hz in all channels. In particular, robust neuronal firing patterns at 0.030 Hz occurred in Ch 9 and 13-16 **(Figure 6b).** These findings suggest that musical pieces with different characteristics result in a neuronal firing rate that exhibits high contrast between the midline and lateral regions of the PFC.

Negative effect of music on autonomic cardiac function and SpO2 levels

To examine whether music affects autonomic cardiac function

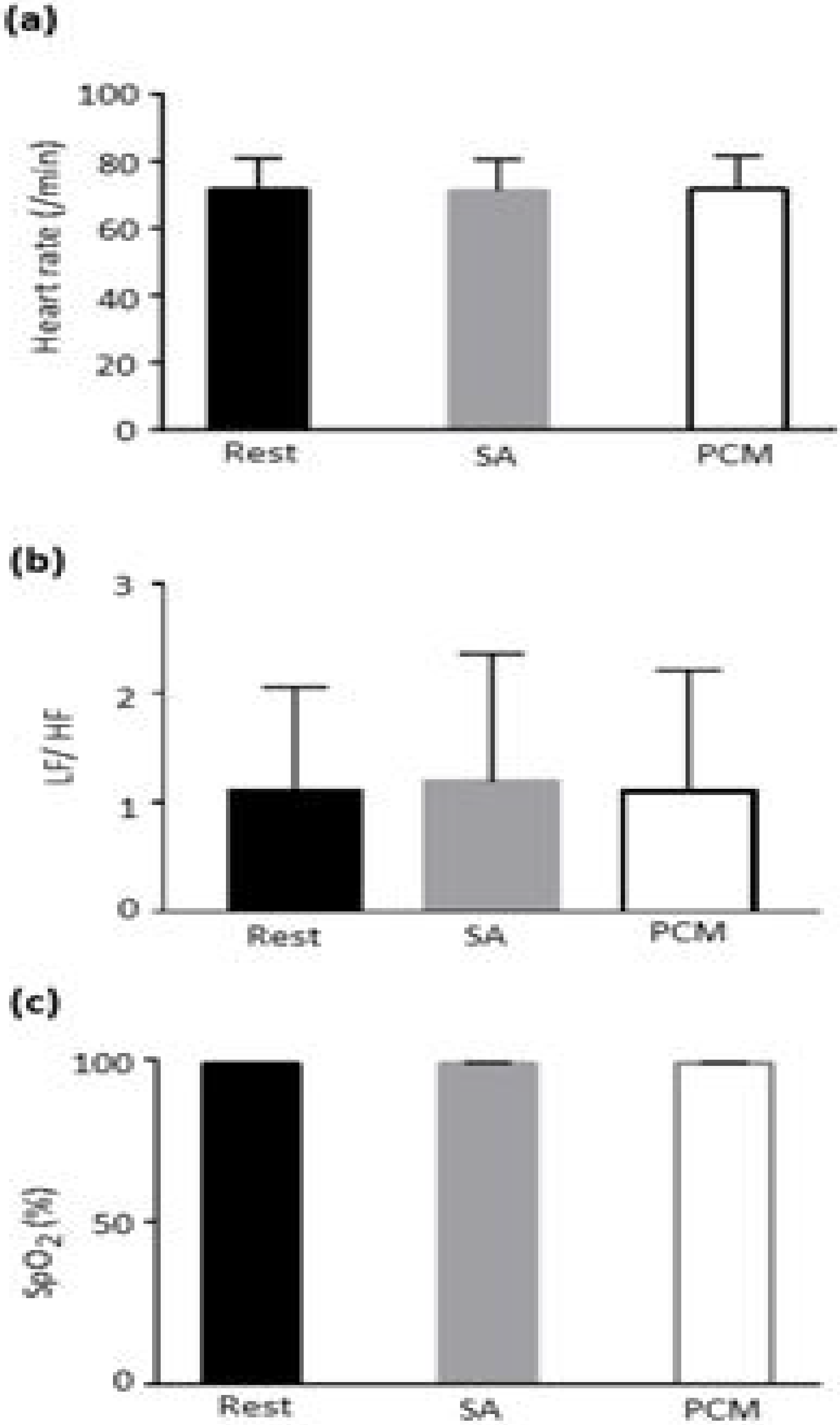

Figure 7 **Physiological parameters during music listening.**

Electrocardiography was used to determine

a) Heart rate variability.
b) The low frequency (LF)/ high frequency (HF) ratio. Pulse oximetry was used to evaluate percutaneous arterial blood oxygen saturation.
c) The musical stimuli had no effect on any of these physiological parameters. Average values for resting and listening to music. SA: "Salut d'Amour"; PCM: "Pomp and Circumstance Marches"; n=14.

as previously described [32,33], we measured heart rate variability based on average heart rate and LF/HF values for all participants **(Figures 7a and 7b).** Relative to the resting state (71.5+2.22 bpm), no significant alterations in heart rate occurred during music listening ("Salut d'Amour", 71.1+2.23 bpm, p=0.89; "Pomp and Circumstance Marches", 71.6+2.33 bpm, p=0.90, n=28). In addition, we observed no significant differences in LF/HF (i.e., an indicator of mental stress) between "Salut d'Amour" (1.12+1.08, p=0.87) and "Pomp and Circumstance Marches" (1.03+1.10, p=0.95) relative to values obtained during the resting state (n=28). All participants exhibited normal SpO2 levels (i.e., oxygen metabolism) during the experiment **(Figure 7c)**, resting state, 99.7+0.31%; "Salut d'Amour", 99.2+0.27%, p=0.48; "Pomp and Circumstance Marches", 99.0+0.11%, p= 0.49, n=28). These findings suggest that autonomic cardiac function was unaffected during music listening.

Discussion

In the present study, we examined whether the complexity of musical pieces (e.g., high pitch, tone, large number of instruments) results in differential alterations in brain activity within the PFC. Different patterns of PFC activity were observed when participants listened to "Salut d'Amour"-which is characterised by a single instrument, a narrow range of musical tones, high acoustic pressure and the "Pomp and Circumstance Marches", which is characterised by 25 instruments, a wider range of musical tones, and lower acoustic pressure at the same sound frequency when compared with "Salut d'Amour". Our fNIRS data revealed that ΔOxy-Hb, a hallmark of brain activity, was profoundly increased and subsequently decreased at every channel when participants listen to "Pomp and Circumstance Marches". Moreover, Oxy-Hb was significantly reduced in the dorsolateral region relative to levels observed in the midline area, suggesting that "Pomp and Circumstance Marches" induced activity within the orbitofrontal cortex.

Several previous studies have suggested that music and sounds in particular activate auditory neurons in the primary auditory cortex during the informational processing of musical tones [34-36]. During these processes, music is encoded into neuronal firing patterns in the thalamus and auditory cortex [37]. In addition, the limbic region of the brain is known to mediate the association between musical and emotion [38]. Thus, our findings support the notion that sounds trigger neuronal activity in brain regions involved in auditory and sensory function, and that these functions eventually affect activity in the PFC. Indeed, previous studies have reported that patients with amusia (i.e., inability to perceive musical pitch) predominantly exhibit a lack of prefrontal activity during music listening [39]. The orbitofrontal cortex and dorsolateral PFC are involved in processing emotions associated with pleasant or unpleasant feelings during music listening [40], while the lateral PFC is critical for auditory attention [40]. In addition, our group previously reported that PFC activity is critical for the determination of pleasant or unpleasant feelings [23]. In the present study, we observed significant differences in Oxy-Hb levels for the orbitofrontal cortex and lateral PFC when participants listened to "Pomp and Circumstance Marches". Hence, our present findings indicate that musical pieces with different properties ("Salut d'Amour" and "Pomp and Circumstance Marches") induce distinct effect on brain function that can be explained by the neuro circuitry models of the PFC.

We also observed different patterns of brain activity including the range of 0.015-0.030 Hz using wavelet analyses. Previous brain imaging studies have indicated that the orbitofrontal cortex oscillates while participants are playing a musical piece (i.e., Antonio Vivaldi's Allegro from Concerto No. 1 in E Major, Op. 8, RV 269, "Spring") [41]. In addition, several lines of evidence suggest that these slow wave oscillations occur during memory consolidation in the hippocampus [42]. Although the properties of musical pieces used in previous studies differ from those of the pieces used in the present study, our findings are consistent with those of previous researchers. Although these results may be explained by music memory, further studies are required to more fully elucidate the neuronal processes associated with music listening.

Music exerts various effects on human psychological and mental states during development. For instance, music listening during preverbal infant stages changes the haemodynamic activity of the neocortical brain and may enhance emotional sensitivity [43]. In addition, music serves as an effective therapy for various mental illnesses due to its relaxing effects: Various studies have reported that music listening can enhance cognitive function [44], improve quality of life, [45] reduce pain [46,47] and improve outcomes in patients with dementia [48] and mental illness [49,50]. Thus, future studies should aim to identify the neural correlates of the effects of music on mental health.

Finally, the present study possesses a limitation of note. Because the distance between the illuminator and detector of the NIRS apparatus was 3 cm, the spatial resolution of the data was limited to 3 cm. Music is usually harmonious, and it is difficult to interpret the findings due to the complexity and length of such music. 28 participants enrolled in this study; however, the sample size is still somewhat low. Future studies should evaluate these points in further detail.

In conclusion, the findings of the present study demonstrated that different musical stimuli exert differential effects on patterns of neural activity in the PFC. These patterns may shed light on the mechanisms underlying music processing in the brain, and the overall role of music in promoting mental health and various cognitive functions. Future studies should aim to determine whether patterns of PFC activity during music listening can be used to monitor mental states in humans.

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