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Institute of Neuroscience (IoNS)
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EXPERIMENTAL RESEARCH

Exploring Human Sensory Cortex Using the New Oddball Design by Frequency-Tagging

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General introduction

Since the eighteenth century, the brain has been approached as the organ of consciousness in its material (anatomical) and functional (physiological) aspects. But since the 1950s, there has been very quickly an integration of different disciplines, ranging from neuro-anatomy to neuroimaging or even neuro-informatics. After researches laid the foundation for neural functioning, new themes emerged regarding brain development, study of consciousness, and cognition understanding. Even in ancient times, it was at least known that human consciousness was permitted, at least in part, by the notion of the senses. Since then, studies by Korbinian Brodmann (1909) and, later, Mountcastle (1998), have demonstrated the existence of spatially and functionally distinct brain areas, including the sensory cortex. It was therefore known that sensory information was processed and perceived by the brain at specific locations while ignoring the underlying mechanisms of these treatments.

As structural studies evolve, new in vivo recording techniques have improved the understanding of neuronal and cerebral function in recent years. The appearance of electroencephalography was a first revolution in the exploration of cognition while the recording of action potentials by the unit stimulation of neurons or the direct cortical stimulation used by Penfield to draw his famous homunculus in 1937 were invasive and not allowing an overview of the activity of the nervous system. Several studies have ventured into early brain mechanisms to understand the neural processing of environmental information, including sensory information. While functional magnetic resonance imaging has the best spatial resolution at the expense of temporal resolution, EEG recording excels in temporal resolution.

The brain activity recorded by EEG involves a large population of neurons (spatial summation) as well as their synchrony (temporal synchronization) in order to have an effective spatial summation. Another benefit of EEG was the lack of necessary collaboration of the patient or participant in the neuroscientific experiment. But the electrophysiological recordings on the scalp revealed ongoing endogenous brain activity, unrelated to the stimulation generated by the environment. This is why these recordings are characterized by a multitude of fluctuations covering all time scales. An additional bias is thus created in this technique, making it problematic to link a specific aspect of a stimulus to its specific brain response, especially since this response is small and can be overlapped by the response to other aspects of the same stimulus, or if the presentation time is too short.

In order to overcome this limitation, the experimental method of frequency-tagging has been posited. This method consists in identifying the specific brain responses to the stimulation sets according to their expected frequencies and determined by the structure of the stimulus. In other

words, a stimulus presented with a specific temporal coding (for example, periodic modulation of luminance of visual objects or periodic modulation of the amplitude of sounds at a given frequency determined by the experimenter) can trigger locked brain responses at the stimulus presentation rate or certain harmonics (the harmonic frequencies are positive integers multiple of the fundamental frequency of a periodic wave). Indeed, assuming that the temporal course of a stimulus is systematically periodic, we can suppose that the neuronal population coding for this stimulus also oscillates with the same period. The frequency of the stimulus thus provides a frequency "tag" to identify the associated brain response. The frequency spectrum of the obtained brain response shows a peak at the specific fundamental frequency and certain harmonics. Indeed, this approach exploits the fact that when a neural response is periodic, it can be represented as a Fourier series, whereas noise is equally distributed in the spectrum (Chemin et al., 2018¹). Hence, frequency tags elicit steady-state evoked potentials (SS-EPs, Steady-State Evoked Potentials: cerebral activity concentrated at a particular frequency in response to a periodic stimulation rate), which essentially means that the same frequency of stimulation can be found in brain responses. To analyze these responses, we must therefore look at the frequency domain and, thanks to this method, we can easily dissociate the specific brain response to the stimulus appearing as a peak on the EEG signal compared to the broadband endogenous activity. Frequency-tagging therefore has a very important signal-to-noise ratio (SNR), which favors the exploration of cortical activities with better accuracy. This has led to a rich literature on steady-state brain reactions in several brain systems studies (for example: Ding et al., 2006²; Bohórquez et al., 2008³; Parkkonen, et al., 2008⁴; Vialatte et al., 2010⁵). However, the study of evoked potentials by EEG requires repetition and averaging of the tracing. The ideal is therefore to increase the signal by preserving this repetition of the stimulus. It was noted that a new experimental design, known as the oddball paradigm, in which one stimulating item appears infrequently within series of standard stimulating items thus showing unexpected stimulatory events in a series of identical stimuli (Huettel et al., 2004⁶), induced larger stimulus-specific neuronal responses. This is also consistent with the fact that fMRI and MEG demonstrated that the repetition of the same stimulus induces a selective decrease in the evoked responses. Moreover, in this new experimental design, the temporal course of the presentation of the stimulus is systematically periodic. In this design, it is assumed then that the neural population coding for an oddball stimulus will also oscillate with the same period. This is typically a reflection of a frequency-tagging method. Recently, several studies (for example: Liu-Shuang et al., 2013⁷; Rossion 2014⁸; Dzhelyova and Rossion 2014⁹; Lochy et al., 2015¹⁰; Rossion et al., 2015¹¹; De Heering and Rossion, 2015¹²) have attempted to combine the dual frequency-tagging / oddball paradigm approach thus benefiting from the double advantage of

high signal-to-noise ratio responses and more objective identification of stimulation contrast response based on the expected frequency of the oddball occurrence.

Intrigued by the discovery of new fields still little explored such as the somatosensory cortex and with the aim of deepening already published works, we plan to forward in the same methodological line as a result of these works. Using the oddball paradigm by frequency-tagging would allow to highlight specific responses to contrasts as fine as a vibrotactile spectro-temporal contrast in somatosensory cortex or a quarter-tone contrast in auditory cortex, in fast sequences, in order to experiment this novel method by exploring unclear remaining fields. Using four distinct experiments, we register by EEG SS-EPs responses corresponding to a stimulus. In the three first experiments, we use a vibrotactile stimulus for somatosensorial cortex exploration. In the last experiment, we use an auditory stimulus for auditory cortex exploration. These experiments aim to study the new oddball design in two different sensory modalities but each one based on vibration-type dynamic inputs (vibration of the skin and vibration of the eardrum). The vibrotactile studies aim to demonstrate that this design is usable in the vibrotactile sensory modality, even for complex contrasts such as spectro-temporal contrasts, natural textures and somatotopic maps convergence. The auditory study tests the impact of periodic design predictability in contrast responses with a frequency-tagging approach.

Experiment 1: Clarifying the encoding of tactile salience and fine-grained texture in the human somatosensory cortex

Abstract

Everyday life confronts us inevitably to the sense of touch. It is this sense which draws the dimensions and the natures of things based on the different contrasts around us, thus playing an essential role in our survival. However, the neural processing of vibrotactile contrast remains largely unknown, probably due to the lack of methods to objectively dissociate the response components specifically related to the contrast from the other components in response to the exploration of textures. To overcome this issue, we tested a novel use of the frequency-tagging approach allowing contrast-specific neural responses to be tracked based on their expected frequencies. Using 2 experimental parts, the EEG was recorded while participants received 40 s sequences of vibrations presented at 8 Hz. A vibro-frequency or fine-grained contrast was embedded every fifth textural item (AAAAB), such that a response observed in the EEG at exactly $8 \text{ Hz}/5$ (1.6 Hz) or harmonics should be the signature of contrast processing by higher neural populations. Contrast-related responses were successfully identified, even in the case of small frequency contrasts or fine-grained texture contrasts (part 1). Moreover, analysis of the brain responses topography revealed the direct implication of the primary somatosensory cortex S1 in the treatment of such signals (part 2). Overall, this new combination of frequency-tagging with an oddball design provides a valuable complement to the classic, transient, evoked potentials approach, especially in the context of vibrotactile information. Specifically, we provide objective evidence on the neural processing of vibrotactile frequency or fine-grained contrast.

Introduction

Goal of project: Touch is one of the five essential senses for the survival and development of living beings as well as for basic social phenomena. It is indeed necessary for the exploration of the environment or objects, essential for equilibrium and locomotion, for grasping and nutrition, etc. It is the mystery of its extreme complexity that makes it all the more intriguing. At a peripheral level of the body, the tactile information is captured by mechanoreceptors of different families. These skin mechanoreceptors distinctly isolate the different vibrotactile contrasts. The mechanoreceptors have preferential frequency bandpass, with fast adapting receptors type I responding preferentially to frequencies below 50 Hz of vibration and fast adapting receptors type II responding preferentially to frequencies above 50 Hz. Based on this, it could be hypothesized that cortical activity recorded to vibrotactile frequency contrast

between two successive inputs would be observed only when the successive inputs are processed by these two separate types of receptors at the periphery. And in fact, this is a little bit what we find in the auditory system, where sounds are easily segregated from each another within a stream of successive auditory inputs when the successive inputs are processed by different frequency channels at the level of the cochlea. But in contrast, we can suppose too that these EEG responses to frequency contrast do not follow only these peripheral constraints and that this contrast encoding operate at higher, central, or cortical level. The study aims to discover this potential higher-level component of vibrotactile contrast information processing.

State of the art: Several studies aimed at characterizing the SS-EP related to the perception of vibrotactile sensations (Colon et al., 2012¹³). However, at least to our knowledge, there is no EEG studies having explored vibrotactile contrast such as contrast of frequency texture or contrast of fine-grained texture. From a mechanical point of view, all we know since Katz's work is that perception of texture relies on two sets of cues: spatial and temporal, and that vibrotaction is essential for perception of this kind of textures (Katz, 1925¹⁴). From anatomical point of view, S1 is known for processing low-level tactile information. It discriminates textures, sizes and shapes of objects. On the other hand, it is conceived that S2 might be responsible for processing and integrating the different modalities of a tactile stimulus, in addition to the consolidation of learning and memorization. Finally, it has recently been proposed that the insula is the brain area which play the role of contrast, or saliency detector (Menon and Udin, 2010¹⁵). Addressing the question of the neural processing underlying vibrotactile contrast, this experiment tends to provide new insights on vibrotactile perception in humans.

Reason of interest: Our main goal is to pierce the world of cortical encoding of vibrotactile information. In this first experiment, we used a fast-periodic oddball design to try to elicit an EEG response related to vibrotactile contrasts. It is an experimental design already used by Nozaradan et al., 2017¹⁶ in the auditory modality to investigate auditory stream segregation and frequency contrast detection. It is also inspired by studies in the visual modality from Rossion et al. who succeeded to capture EEG responses to contrasts related to the perceptual categorization of different faces independently of low-level visual contrasts. We hypothesize here that EEG responses to frequency contrast do not follow the peripheral constraints due to mechanoreceptors of skin. For instance, we suppose that we may observe different forms of EEG response for different natures of vibrotactile contrast, such as contrast of frequency versus contrast of fine-grained texture. To the extent that our hypothesis is the right one, it is interesting to know whether these EEG responses come from S1, S2, the insula, etc. In the same time, we

may check the relation between these EEG responses and the perception of the vibrotactile contrast by the participant.

Part 1: Simultaneous bimanual stimulation

Aim: Test the recording of cortical response to vibrotactile contrast with human scalp EEG and understand the characteristics of these responses (nature, mechanism, and cortical origin).

Participants: 9 participants between 25 and 50 years old without neurological and/or psychiatric disorders have been recruited for this experiment. All the data were interpretable. There were no participant's data rejection.

Vibrotactile stimulus (figure 1): The stimulus consists of 8 distinct vibratory sequences divided in 4 experimental conditions. Vibration sequences are during 40 s. They respect the oddball paradigm in which one stimulating item appears infrequently within series of standard stimulating items. Each sequence is made up of alternation of both A and B items following the AAAAB structure. Hence, A stands for standard stimulating item and B stands for the oddball stimulating item. This oddball method and the AAAAB design allow us to dissociate neural responses to tactile inputs (frequency corresponding to the onset frequency of the inputs along the sequence) from neural responses specific to the processing of the contrast between the items A and B. Each A and B item lasts 125 ms and is therefore characterized by a frequency equal to 8 Hz (f_{pr} : item base rate). Appearing in the 5th position, the B item is characterized by the oddball appearance frequency $f_B = f_{pr}/5 = 1.6$ Hz. The sequences of the stimulus are programmed using MATLAB and are transmitted to the participants via haptuators. In the 1st condition, there is no contrast between A and B. It gathers the first three sequences (s1, s2 and s3) in which the carrier frequency of A is equal to the carrier frequency of B: 48 Hz in s1, 144 Hz in s2 and 200 Hz in s3. Therefore, these sequences do not simulate frequency or fine-grained texture contrasts. As possible peripheral target of these vibrotactile inputs, it can be supposed that the sequence at 48 Hz carrier frequency (s1) will be preferentially processed by the fast adapting mechanoreceptors type I of the skin. And in contrast, it can be supposed that the sequence at 144 Hz carrier frequency (s2) and 200 Hz carrier frequency (s3) will be preferentially processed by the fast adapting mechanoreceptors type II of the skin. In the 2nd condition, there is a small contrast between A and B. It gathers the fourth (s4) and the fifth (s5) sequences where A and B differ by 56 Hz. Their carrier frequencies equal 144 Hz (A in s4 and B in s5) and 200 Hz (B in s4 and A in s5) in these sequences. Therefore, these sequences are characterized by a small frequency contrast between the A and B items. And in these two cases, both items A and B are supposed to be preferentially processed by fast adapting mechanoreceptors type II of the skin. In the 3rd condition, we find a larger contrast between A

and B elements than in 2nd condition. The 3rd condition gathers the sixth (s6) and the seventh (s7) sequences in which A and B differ by 152 Hz. Their carrier frequencies equal 48 Hz (A in s6 and B in s7) and 200 Hz (B in s6 and A in s7) in these sequences. Therefore, these sequences are characterized by a large frequency contrast. And in these two cases, items A and B are supposed to be preferentially processed by fast adapting mechanoreceptors of the skin type I for 48 Hz elements and II for 200 Hz elements.

It is important to specify that these frequency contrasts may engender intensity contrasts too, hence the use of “saliency contrast” to synthesize this effect (Birnbaum et al., 2007¹⁷). Thereby, if the 1.6 Hz oddball SS-EP related to the detection of a contrast of frequency is observed, this response could also reflect the detection of a contrast of saliency across the two items. Indeed, this contrast of saliency could be due to the actual different frequencies, so the different number of cycles of vibrotactile stimulation of the skin per second. So, in this case, a stimulus at 200 Hz is expected to provide more energy of stimulation of the skin than a frequency of 48 cycles per second. A second reason for this contrast in saliency related to a contrast of frequency is due to the different properties of the skin mechanoreceptors. And in this sense, psychophysical studies have shown that a vibrotactile stimulus at 200 Hz is perceived as more salient than a stimulus at 144 Hz and 48 Hz (Cholewiak, 1979¹⁸). It is important too to observe that in these three conditions, the spectrum of the envelope of the vibrotactile input only exhibits peaks at 8 Hz and harmonics, so corresponding to the presentation rate of the items in the sequences. This 8 Hz frequency corresponds to the 125 ms duration of each item in the sequences. But there is no peak at 8 Hz divided by 5, so corresponding to the occurrence of the item B in the sequences with frequency contrast (see figure 2).

We had also a 4th condition in which the items A and B were two different white noise bursts of 125 ms. By using these white noises, we actually controlled for all the biases inducing a saliency contrast. The 4th condition boils down to the eighth sequence (s8) where A and B are not carried by specific frequencies. The two items are represented here by two distinct Gaussian noises (white noises), respecting A and B. Therefore, this sequence is characterized by a fine-grained texture contrast between the A and B items. Here, the items A and B have the same frequency content, the same spectral power density, the same envelope, and they are processed by the same receptors at the peripheral level. So that if there is a response to the contrast between A and B, this must be due to a fine-grained spectro-temporal encoding of the inputs. And this is what we can call a contrast of fine-grained texture.

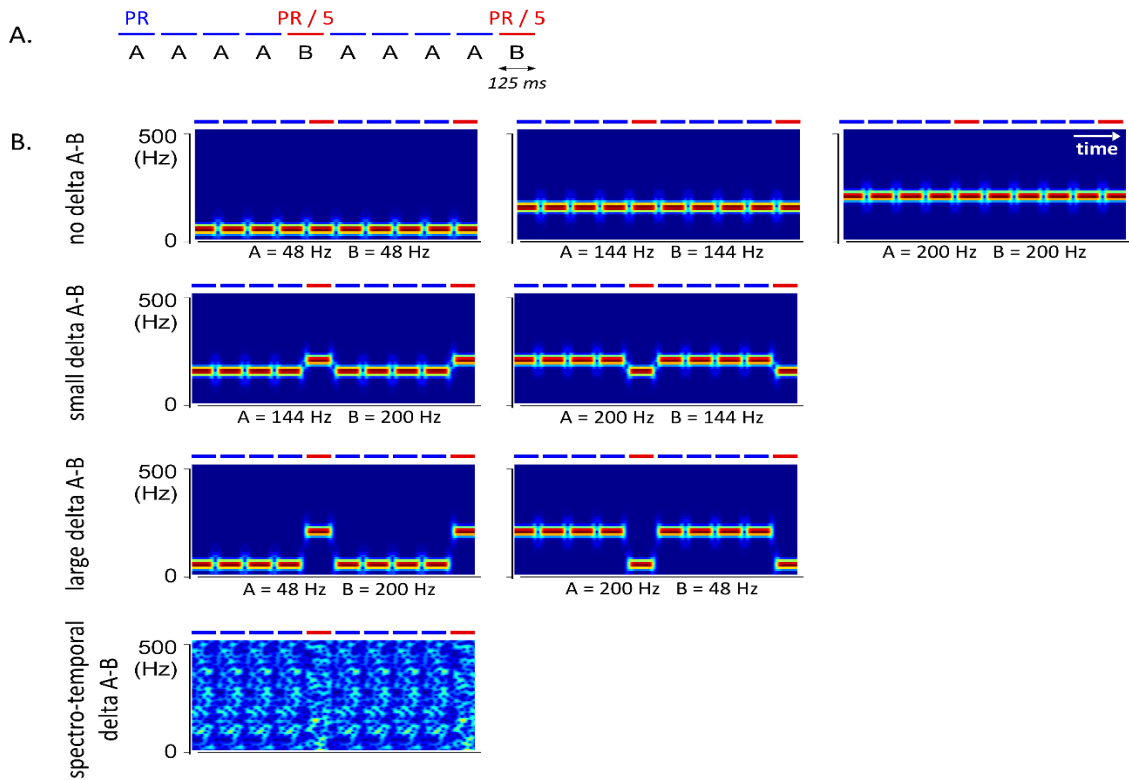


Figure 1. Vibrotactile stimuli. Participants were stimulated with distinct sequences of two repeated vibrotactile stimuli, A and B. These sequences were transmitted by two haptuators held between the tips of the index finger and the thumb of left and right hands concomitantly.

A. Structure of the sequences. Every fifth stimulus, stimuli B were interspersed between stimuli A, and this pattern was repeated during 40 s. The presentation rate (PR) corresponds to the repetition rate of the vibrotactile stimuli in the sequence (stimulus duration = 125 ms; $f_{PR} = 8$ Hz); the repetition rate of the stimulus B corresponds thus to the fifth of the presentation rate ($f_{PR}/5 = 1.6$ Hz).

B. Time-frequency map of the four sequences. In the first three sequences, A and B consisted of frequencies at either 48 Hz, 144 Hz or 200 Hz. In condition 1 (first row), the difference between stimuli A and B (delta A-B) was equal to 0. In condition 2 (second row), delta A-B was equal to 56 Hz, so that stimuli A and B can be assumed to be specifically processed by the same type of skin mechanoreceptors (rapidly adapting type II or Pacinian corpuscles). Importantly, participants could discriminate stimuli A and B. In condition 3 (third row), where delta A-B was equal to 152 Hz, participants could also discriminate stimuli A and B. This time, stimuli A and B can be assumed to be processed by distinct skin mechanoreceptors (rapidly adapting type I and type II mechanoreceptors). In condition 4 (fourth row), A and B consisted of two distinct Gaussian white noises, thus resulting in a complex spectro-temporal delta A-B. In this condition, A and B are assumed to be processed by the same mechanoreceptors, as the spectral distribution of the two stimuli is equivalent. However, participants could not discriminate stimuli A and B.

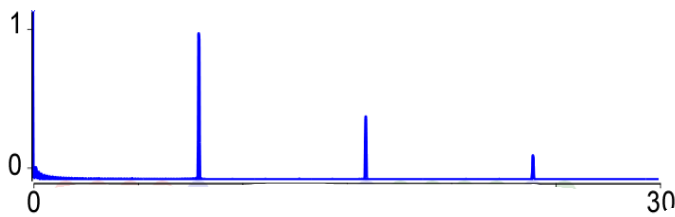


Figure 2. EEG global field amplitude spectra. Spectrum of the envelope of all four sequences (blue spectrum). In all conditions, there is a clear peak at 8 Hz and harmonics (corresponding to the presentation rate of the stimuli in the sequences) but no peak at 1.6 Hz (corresponding to the occurrence of stimulus B every five stimuli ($pr/5$)).

Experimental conditions: Each vibrotactile sequence is sent concomitantly to both hands. The vibration transmission is ensured by 1 haptuator in each hand, stuck between the pulps of thumb, index and middle finger. The 4 stimulatory conditions correspond to 4 experimental blocks. The different blocks are applied in random order to the different participants. For the same block, the stimulatory sequences are applied in ascending numerical order. Once the first, the second or the third block is triggered, it is repeated 4 consecutive times. Once the fourth block is triggered, it is repeated 8 consecutive times. During all stimulations, the participant is subjected to listening to white noise in order to avoid biasing the results by auditory perception of the stimulus. For optimum participants' attention, they are asked to properly focus on the stimulus. At the end of each trial, the participants must report any variation in rhythm and/or intensity in the sequence and describe the felt stimulation.

Expected observations: Based on the experimental design, the analytical procedure combines the advantages of the frequency-tagging approach with an oddball paradigm. This new design was proposed as a powerful method to capture contrast responses with a high signal-to-noise ratio and more objectively, based on the expected frequency of this contrast responses.

The first part of the observations involves the frequency domain. First, we expect to find in the 4 conditions peaks of EEG response at $f_{pr} = 8$ Hz and harmonics, thus corresponding to the presentation rate of each item in the sequences. But more importantly, concerning the first three conditions, we hypothesize to observe an additional peak of EEG response elicited precisely at 8 Hz divided by 5, so $f_B = 1.6$ Hz and harmonics, thus corresponding to the occurrence of the item B in the sequences with frequency contrast, either in the 3rd condition only, or in the 2nd and 3rd conditions. An EEG response observed at 8 Hz/5 and harmonics should correspond to a neural response specifically related to the contrast (“contrast response”) between A and B (De

Heering and Rossion 2015¹²; Liu-Shuang et al., 2013⁷; Rossion 2014⁸). Again, this 1.6 Hz is the expected frequency of the oddball in the sequence.

If the oddball response is observed in the 3rd condition only, this would mean that the contrast detection is likely to be constrained by a peripheral encoding of the frequency contrast, when the two items are processed by distinct mechanoreceptors of the skin. But in contrast, if the oddball response is observed already in the 2nd condition, this would mean that the contrast detection is likely to be constrained by a central encoding of the frequency contrast, independently of the peripheral constraints. And importantly, by estimating the spectrum of the envelope of the vibrotactile input (figure 2), we ensure that if we find a peak at the oddball frequency, it cannot be an electrical artifact due to the stimulation device, which is always an issue with such device. Concerning condition 4, the 1.6 Hz and harmonics peaks on the EEG spectrum would confirm, combined to the other results, the fine-grained spectro-temporal encoding of the inputs.

The second part of the observations involves topographical mapping of cerebral activity related to the sequences received by the participant. We expect that the neuronal activity be concentrated in the external part of parietal cortex with a bilateral topography because of the simultaneous stimulation of both hands, thus compatible with cortical activity from S1. To plot the topographies, we used an Fz reference (Fz is the ground reference point for all EEG electrodes), because this reference is known to efficiently capture activity originating from S1 in response to tactile stimulation of the hand, by concentrating this activity on parietal electrodes.

EEG recording: The participant is comfortably seated in a chair. We instruct him to focus on a point during the recording to improve the signal/noise ratio. 64 Ag-AgCl electrodes according to the 10/10 International System provide registration. Eye movements are also monitored (2 electrodes vertically, 2 electrodes horizontally) to facilitate the analysis by taking them into account. The impedance of the electrodes is lowered to below 10 k Ω .

EEG processing: The EEG processing stages are performed by the Letswave5 and Letswave6 functions running in MATLAB. The continuous EEG recordings are filtered using a 0.1 Hz high-pass Butterworth zero-phase filter to remove very slow drifts in the recorded signals. Epochs lasting 40 s, periods of EEG corresponding to the application of the stimulus, are obtained by segmenting the recordings from 0 to 40 s relative to the onset of the vibrotactile stimulus. When necessary, artifacts produced by eye blinks or eye movements are removed from the EEG signal in the different epochs thanks to a validated method based on Independent Component Analysis, using the runica algorithm. For each subject and condition, EEG epochs are averaged across trials. The time-domain averaging procedure is used to enhance the

signal/noise ratio of EEG activities time-locked to the patterns while cancelling out background noise not aligned to the stimulus across trials. The resulting average waveforms are then transformed in the frequency domain using a discrete Fourier transform. It yields a frequency spectrum of signal amplitude (μV) ranging from 0 to 500 Hz with a frequency resolution of 0.025 Hz (i.e. 1/40 s; the frequency resolution being the inverse of the duration of the temporal window on which the Fourier transform is calculated, here 40 s.). Within the same frequency spectra, the signal amplitude may reflect the SS-EPs elicited by the stimulus and also unrelated residual background noise due, for example, to spontaneous EEG activity, muscle activity or eye movements. To get valid SS-EPs estimates, the contribution of this residual background noise is considerably alleviated by subtracting, at each bin of the frequency spectra (abscissas of frequency spectra), the average amplitude measured at surrounding frequency bins (2 frequency bins ranging from -0.12 to -0.072 Hz and from 0.072 to 0.12 Hz relative to each frequency bin), for each participant, condition and electrode. The validity of this subtraction procedure relies on the assumption that, in the absence of an SS-EP, the signal amplitude at a given frequency bin should be similar to the signal amplitude of the mean of the surrounding frequency bins (Chemin et al. 2014¹⁹; Mouraux et al. 2011²⁰; Nozaradan et al. 2012²¹, 2015²²). This subtraction procedure is also important to assess the scalp topographies of the elicited SS-EPs, as the magnitude of the background noise is not equally distributed across scalp channels. The resulting amplitude values are further used to compare the amplitude of SS-EPs elicited at f_{pr} and at f_B and its harmonics (i.e. $2f_B$, $3f_B$, etc.).

Results: We analyzed the responses in the frequency domain (figure 3) and by topographical maps (figure 4). For all experimental conditions, a base EEG response is expected at $f_{pr} = 8$ Hz and harmonics ($2f_{pr} = 16$ Hz and $3f_{pr} = 24$ Hz), corresponding to the response to the individual items making up the sequences with an inter-onset interval of 200 ms (i.e. a frequency of 8 Hz). In condition 1, all participants systematically report a greatest saliency for the stimulus at 144 Hz, and then at 200 Hz and then at 48 Hz. The amplitude of EEG responses tends to follow the perception of the participants in term of saliency: 144 Hz > 200 Hz > 48 Hz. This might be an influence by the haptuator device itself. Indeed, the haptuators that we used are known to present a tuning curve for the transmission of the vibration, which could counterbalance the biases toward the highest frequency, here 200 Hz, by amplifying vibration at 144 Hz.

In 2nd and 3rd conditions, we observe clearly in the EEG frequency spectra an oddball response at $f_B = 1.6$ Hz and harmonics ($2f_B = 3.2$ Hz; $3f_B = 4.8$ Hz; $4f_B = 6.4$ Hz). These oddball and harmonics responses are enhanced when the most salient item is the oddball (i.e. for s5 with A = 200 Hz and B = 144 Hz in condition 2, and for s6 with A = 48 Hz and B = 200 Hz in condition 3). In condition 3, extra unexpected observations add themselves to that previously seen. We

find relatively pronounced peaks at the harmonics 11, 12, 13, 14 and 16 of f_B (1.6 Hz), the 15th harmonic neglected because merging with the third harmonic of the $f_{pr} = 8$ Hz ($3f_{pr} = 15f_B = 24$ Hz).

Interestingly, in condition 4, the contrast of spectro-temporal content was not perceived by the majority of the participants (only 2 participants perceiving a contrast). But curiously, only high frequency oddball responses are captured on the EEG spectrum corresponding to the f_{pr} harmonics 11, 12, 13, 14 and 16.

In terms of topography, we observe a bilateral parietal topography for base EEG response (8 Hz and harmonics) in each condition with no frontocentral activity, which is typical to Fz reference and activity in response to tactile stimulation of the hand. For the oddball EEG response (1.6 and low harmonics), the same bilateral topography is observed in all conditions except for condition 4 where there is no significant response. Finally, the high frequency oddball responses found in conditions 3 and 4 follow also the same bilateral topography and are larger in the 4th condition.

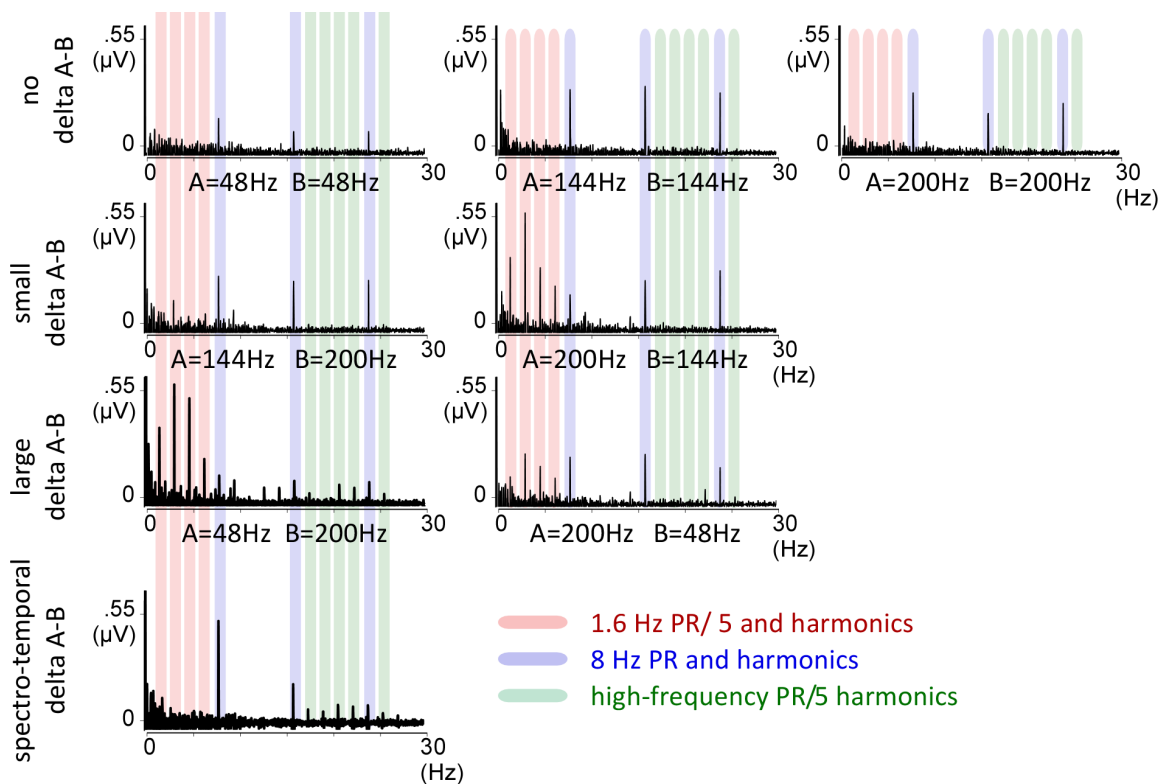


Figure 3. First to fourth row. The EEG spectra were obtained after averaging across participants (N=9) and the 64 EEG electrodes. In the four conditions (first to fourth row), a steady-state evoked potential (SS-EP) was observed at 8 Hz, corresponding to the presentation rate (pr) of the stimuli in the sequence (highlighted in blue). In condition 2 (row 2), in which delta A-B was 56 Hz, an additional SS-EP was elicited at 1.6 Hz and harmonics (3.2 Hz, 4.8 Hz, 6.4 Hz) (highlighted in red), corresponding to the occurrence of stimuli B. This additional activity could be interpreted as a response specific to the contrast detection between stimuli A and B. In condition 3 (row 3), in which delta A-B was 152 Hz, the additional SS-EP was again

elicited at 1.6 Hz and harmonics (3.2 Hz, 4.8 Hz, 6.4 Hz), corresponding to the occurrence of stimuli B. Moreover, additional responses emerged at frequencies corresponding to sidebands of the PR third harmonic, i.e. at 24 Hz + -1.6 Hz (highlighted in green). Unlike conditions 2 and 3, there was no significant response at pr/5 frequency and harmonics in condition 4 (row 4), characterized by a spectro-temporal delta A-B. However, the additional high-frequency pr/5 harmonics responses emerged significantly. Note that in condition 4 participants could not discriminate stimuli A and B.

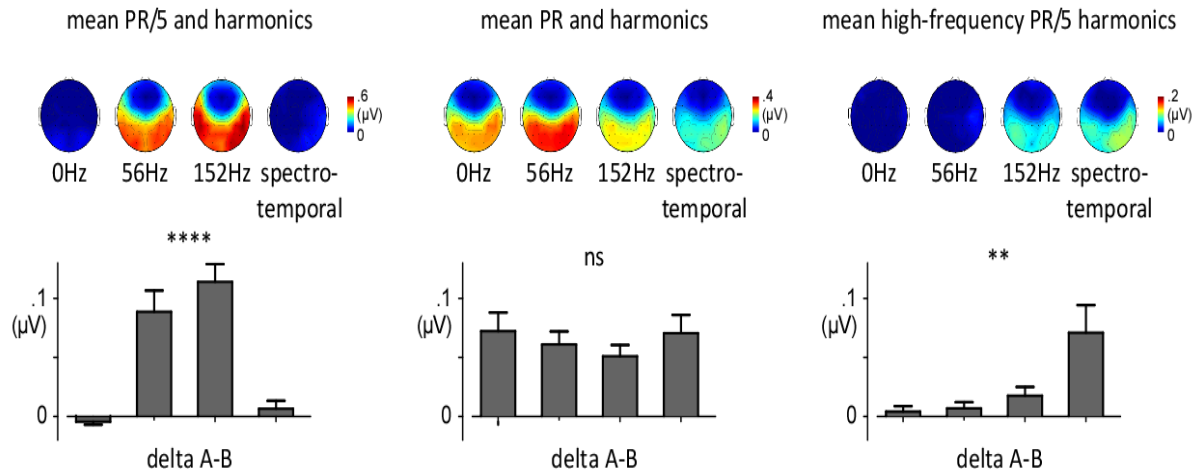


Figure 4. First row. Topography of the SS-EPs (Fz reference) averaged across participants (N=9) for the three groups of responses: pr/5 (i.e. 1.6 Hz and harmonics), PR (i.e. 8 Hz and harmonics) and high-frequency pr/5 (i.e. 24 Hz +-1.6 Hz). A posterior distribution was observed bilaterally, as the finger stimulation was at left and right hands simultaneously. This topography is compatible with activity from S1. Across conditions, these responses differed only in amplitude but not in their topographical distribution.

Second row. Mean and standard error of the mean across participants for the SS-EP amplitudes obtained for the three groups of response across the four conditions. These values were obtained after averaging across the 64 electrodes. For the pr/5 group (1.6 Hz and harmonics), a repeated-measures ANOVA revealed a significant difference across the four condition (****: $p < .0001$), with prominent responses in conditions 2 and 3, as compared to conditions 1 and 4. In contrast, the PR group of response (8 Hz and harmonics) remained stable across the four conditions. Finally, the high-frequency pr/5 harmonics group showed significant difference across conditions, with prominent amplitudes in the fourth condition (**: $p < .01$).

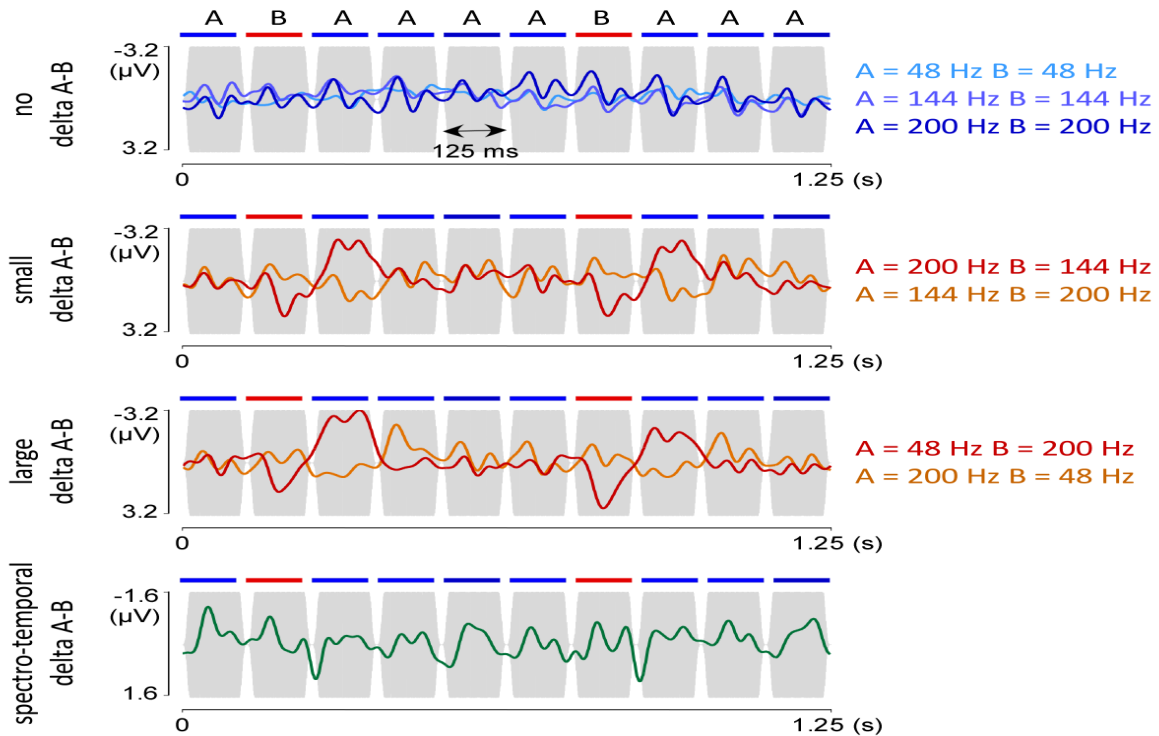


Figure 5. Time course of averaged 1.25 s duration segments (corresponding to the duration of two repeated AAAAB sequences) of the EEG signal obtained at posterior sites (averaged P3 to P8 and PO3 to PO8 electrodes) after band-pass filtering between 0.1 Hz and 30 Hz and averaging across participants, for the four conditions (each type of stimulus sequence presented separately). The grey bars represent the stimuli. In the four conditions, responses to each stimulus were observed, thus corresponding to the 8 Hz SS-EP. An additional response was elicited by tones B in conditions 2 and 3, thus corresponding to the $f_{pr}/5$ SS-EP observed in the EEG spectrum. Note that in both conditions 2 and 3, the response to stimuli B was prominent when B was perceived as more salient than A in the sequence. In other words, in condition 2, the 144 Hz frequency was perceived as more salient than the 200 Hz frequency (this difference can be attributed to the haptuator device favoring frequencies between 100 and 150 Hz according to a Gaussian curve). Additionally, in condition 3, the 200 Hz frequency was perceived as more salient than the 48 Hz frequency. Importantly, in condition 4, response to stimulus B showed a latency delayed of 70 ms as compared to the responses to stimulus B in conditions 2 and 3. This delay in the latency of the response can be interpreted as the time required by the central somatosensory system to accumulate evidence that stimuli A and B present distinct fine-grained spectro-temporal representation.

Interpretation of the results: The results of Part 1 reveal brain activities corresponding to the detection of tactile frequency and fine-grained contrasts. The brain therefore processes, consciously or not, the vibrotactile information related with salience and fine-grained texture. Most importantly, the forms of the response related to frequency/salience vs. fine-grained contrast encoding significantly differ from each other, implied by the different peaks appearance on the EEG spectra across the different conditions, thus indicating that two distinct encoding by the human somatosensory system support these two tactile features. But these different forms of response have the same topography: despite the different encoding type, it is processed within the same cortical region. Moreover, the topographical distribution of these

responses is compatible with activities originating from S1, suggesting that these tactile contrasts are not only processed by high-order somatosensory areas but already in the earliest cortical level of processing of tactile inputs. This last point deserves to be deepened.

Statistical confirmation: see Nozaradan et al., in prep.

Part 2: Stimulation of right hand and right foot

Aim: Test for an S1 somatotopy with responses to frequency and fine-grained texture contrasts.

Participants: 8 participants between 20 and 50 years old without neurological and/or psychiatric disorders.

Vibrotactile stimulus: Here, we use only two stimulatory sequences. They correspond respectively to the 6th and the 8th sequences of part 1 vibrotactile stimulus, i.e. s6 (frequency/saliency contrast) and s8 (fine-grained contrast). It is simply to simulate the two stimulation categories of contrast (frequency/saliency vs. fine-grained texture) that we use only these two sequences. The choice of s6 for the frequency/saliency contrast condition is justified by the net and evident results obtained in Part 1 with sequence.

Experimental conditions: Although the hand is tested in the first experiment, it is important to test it again here to be sure of the contralateralisation of the evoked activities for unilateral manual stimulation. The first experiment stimulating hands bilaterally, we have, by that, to be sure of the contralateralisation of the responses evoked by the stimulation of each hand.

In addition to that, we test in part 2 hand vs. foot, in order to compare the topographies obtained in both conditions. All in all, we get a crossed design tested types of responses (f_B low harmonics vs. high harmonics), stimulatory sequences (s6 vs. s8) and stimulated regions (hand vs. foot). Each vibration sequence of s6 and s8 is sent to the hand or to the foot. The vibration transmission is ensured by 2 haptuators on the right hand. One is stuck between the pulps of thumb and index; the palm maintains the other. On the right foot, the vibration transmission is ensured by 4 haptuators on which softly rest the first three or four toes. This difference in number of haptuators used is explained by the fact that the peripheral receptive fields and the central neurons that encode information about texture are probably not as fine in the foot as in the fingers (Kennedy et al., 2002²³). 4 experimental blocks are established: s6-hand, s8-hand, s6-foot and s8-foot. The different blocks are applied in random order to the different participants. Each block consists in 6 repetitions of the sequence for the s6 stimulus, and in 10 repetitions for the s8 stimulus. During all stimulations, the participant is subjected to listening to white noise in order to avoid biasing the results by auditory perception of the stimulus. For optimum participants' attention, they are asked to properly focus on the stimulus. At the end of

each trial, the participants must report any variation in rhythm and/or intensity in the sequence and describe the felt stimulation sequence.

Expected observations: To determine whether or not the activity originates from S1, we want to test for an S1 somatotopy. To establish an S1 somatotopy, we expect the projection of cortical brain responses for stimulation of the hand to appear on electrodes contralateral to the stimulated hand (parietal area). In contrast, we expect to find the projection of brain responses to a stimulation of the foot on the medial line (central area), with no contralateral distribution. The reference electrode is the virtual average of the recording electrodes. If we use an Fz reference as in Part 1, this reference is likely to cancel out the activity elicited in response to the stimulation of the foot, as this response is expected to project only on the central electrodes close to Fz. This is the reason we use an average reference instead. As demonstrated in Part 1, these brain responses are expected by the appearance of peaks at a frequency equal to the f_{pr} (8 Hz) and at its harmonics in the frequency spectrum of the considered electrodes for all the different stimulus sequences applied. Still based on Part 1 results, we expect the appearance of peaks at a frequency $f_B = 1.6$ Hz and at its harmonics in the frequency spectrum of the considered electrodes for s6 where there is a large difference between the carrier frequencies of A and B items. We may also expect the appearance of the high frequency oddball responses (harmonics 11 till 16) in both sequences as above.

EEG recording and processing: The procedure is the same as in Part 1 (see Part 1 for details).

Results (figure 6): We analyzed the responses by transferring the EEG spectra on topographical maps. In the frequency spectrum, we observe, as expected, a peak at 8 Hz corresponding to the f_{pr} , for all experimental conditions. We also observe its harmonics: $2f_{pr} = 16$ Hz and $3f_{pr} = 24$ Hz.

In addition, in condition s6-hand, we find as expected peaks at 1.6 Hz and harmonics corresponding to the f_B and its harmonics ($2f_B = 3.2$ Hz; $3f_B = 4.8$ Hz; $4f_B = 6.4$ Hz). The previously unexpected high harmonics 11, 12, 13, 14 and 16 of 1.6 Hz are again observed, the 15th harmonic neglected because merging with the third harmonic of the $f_{pr} = 8$ Hz ($3f_{pr} = 24$ Hz). In condition s6-foot, we only find the 1.6 Hz and low harmonics peaks. We do not observe high harmonics in this s6-foot condition.

In the fine-grained texture conditions (s8-hand and s8-foot), the peaks at 1.6 Hz and at its harmonics 2, 3 and 4 are absent. The high harmonics peaks are only observed in s8-hand and are absent from s8-foot EEG spectrum. We draw attention to significant difference in the amplitude of these high peaks between those which respond to an activity linked to s8-hand (much greater) and those having an activity linked to s6-hand (less great).

In summary the peaks at 1.6 Hz corresponding to the f_B and its harmonics ($2f_B = 3.2$ Hz; $3f_B = 4.8$ Hz; $4f_B = 6.4$ Hz) meet our expectations in the frequency spectra generated by salience contrasts (s6-hand and s6-foot) confirming Part 1 results. However, the oddball peaks at 1.6 Hz and at its harmonics 2, 3 and 4 are absent from the fine-grained texture exploration frequency spectra as in Part 1 (s8-hand and s8-foot conditions) as in Part 1. Finally, the high harmonics add themselves to that lower for frequency/saliency and spectro-temporal contrasts detected by the hand (s6-hand and s8-hand) but are undetectable by the foot.

Finally, the topographical representations match with our Part 2 principal hypothesis. For s6-hand and s6-foot blocks, brain activities are respectively centered following an obvious S1 somatotopy. The contralateral centro-parietal topography of the activity for the hand in response to s8 respects the S1 somatotopy of the hand. No significant spectro-temporal cortical activity appears with the unilateral foot stimulation in response to s8.

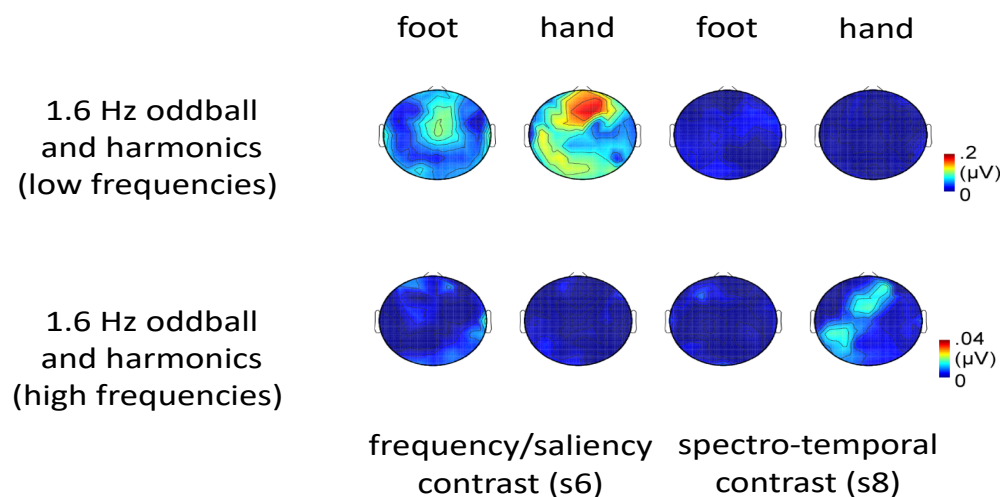


Figure 6. First row. Topography of the SS-EPs (average reference) averaged across participants (N=8) for the oddball and low harmonics responses in the four experimental conditions: s6-foot, s6-hand, s8-foot and s8 hand. A centro-parietal distribution was observed with the s6-foot condition. A left posterior distribution was observed unilaterally with s6-hand condition, as the finger stimulation was at right hand simultaneously. The central brain distribution of the s6-hand condition is due to the averaging reference across the 64 electrodes, yielding topographies including both parietal and central distribution of the activity in response to the vibrotactile stimulation of the hand. This topography is compatible with activity from S1. As in Part 1, there is no signal recorded corresponding to the oddball and its (low) frequencies with the spectro-temporal contrast simulation sequence s8. Across conditions, these responses differed only in amplitude but not in their topographical distribution.

Second row. Topography of the SS-EPs (average reference) averaged across participants (N=8) for the oddball and high harmonics responses in the four experimental conditions: s6-foot, s6-hand, s8-foot and s8 hand. As in Part 1, high harmonics frequencies of the oddball detection are concentrated mostly in the spectro-temporal contrast brain activity related to the hand. A left posterior distribution was observed unilaterally with s8-hand condition, as the finger stimulation was at right hand

simultaneously. The central brain distribution of the s6-hand condition is due to the averaging reference across the 64 electrodes. This topography is compatible with activity from S1. There is no spectro-temporal contrast response for the unilateral foot stimulation. As shown in figure 3, the high-frequency pr/5 harmonics group showed significant difference across conditions, with prominent amplitudes in the s8-hand condition and undetectable responses in the other conditions. Across conditions, these responses differed only in amplitude but not in their topographical distribution.

Interpretation of the results: The resulting topography of s6-hand and s6-foot blocks tracing an S1 somatotopy enables us to conclude in favor of the initial assumption regarding vibrotactile information processing relative to frequency contrast. The fact that the topographical study linked to s8 does not show brain activity for the s8-foot block but only for s8-hand does nevertheless not falsify the initial hypothesis regarding vibrotactile information processing relative to fine-grained texture nor its S1 origin. Indeed, the similarity of the topographical distributions on the scalp for responses to frequency contrast and to fine-grained texture contrast applied on the hand suggests that the two types of responses are from S1. That there are peaks at 1.6 Hz harmonics 11, 12, 13, 14 and 16 in s8-hand frequency spectrum and not at 1.6 Hz and harmonics 2, 3 and 4 shows again a likely difference in the way of encoding fine-grained texture contrasts towards frequency contrasts. On the other hand, that there are no peaks at 1.6 Hz and high harmonics in the s8-foot frequency spectrum means probably that the sensory receptors in the foot are not fine enough to encode the stimulus (see the use of 4 haptators for the foot vs. 2 for the hand because of better encoding resolution in the hand).

Statistical confirmation: See Nozaradan et al., in prep.

Discussion

General conclusion: The frequency-tagging method applied to the new oddball experimental design reveals for the first time an EEG-record of central processing of vibrotactile contrasts on human scalp. This method permitted to investigate with objective measures neural contrast detection in parallel to psychophysics studies (Swets et al., 1969²⁴; Kim et al., 2014²⁵). We can now put forward the higher, central, and cortical level of vibrotactile information processing in human beings and understand that it does not only follow peripheral constraints due to skin mechanoreceptors. This processing takes several forms depending on the nature of the tactile contrast, depending on whether it is a frequency or saliency contrast vs. a fine-grained contrast for example. And this novel method showed too by its fine resolution that the cortical areas responsible for processing vibrotactile information related to salience and fine-grained texture in the hands are the same. The analysis matches them with their S1 counterparts in human beings. The same goes for the processing of vibrotactile information related to salience in the foot as shown in the second part of the experiment. Vibrotactile information related to fine-

grained texture processing validates probably its S1 somatotopy too. This extrapolation is justified in the interpretation of results. The vibrotactile information cortical processing, which is referred to, therefore follows a typical S1 somatotopy. This processing seems to be independent of consciousness, since similar cortical responses have been recorded on participants who perceived the oddballs and others who did not. The statistical confirmation, supported by the non-random nature of the data collected, allows us to conclude definitively for these aspects of vibrotactile information processing, linked to frequency contrast and fine-grained texture, in human beings.

Perspectives: A first level of higher elaboration is highlighted. It is therefore interesting to find out how far the level of processing within S1 can go. This leads to questioning the actual role of S2, or even of its existence in human beings. We seek in the same sense characterizing the emergence of these texture representations from distant interconnected brain areas (for example S2 or the insula). Moreover, the unexpected observations in the frequency spectra of the fine-grained texture stimulation in the hands (first and second experiments) presenting small peaks at harmonics 11, 12, 13, 14 and 16 of f_B are intriguing. It would be interesting to explore them. Another surprising observation takes place during the second experiment, although it is not of primary importance in it: participants with relatively ample peaks in response to the contrast ($f_B = 1.6$ Hz and its harmonics) in s8-hand are those who do not affirm the perception of this contrast when s8-hand is played (parts 1 and 2). In contrast, the participants having relatively short peaks in response to s8-hand are those who perceive easily this contrast when s8-hand is played (parts 1 and 2). This observation invites us to delve the relationship between somatosensory cortex and consciousness. We are interested by this same point in thinking about the possible correlation between amplitude of brain response to frequency and fine-grained texture contrasts and the behavioral measurement of these contrasts.

We plan to repeat these experiences by doing intracranial EEG recordings in patients undergoing an intracranial EEG recording for the diagnostic workup of partial epilepsy. This recording type allows us to refine our interpretations by increasing the data accuracy and by having a better spatial resolution. Thereby, we expect to confirm such inference made about the S1 origin of brain activity relative to fine-grained texture by getting direct answers of S1 via electrodes implanted in the brain. Back to human scalp, it may be interesting, in a perspective of continuing the understanding of the encoding of natural textures by the brain, to characterize the emergence of invariant perceptual categorizations from the finger exploration of natural textures still by frequency-tagging and oddball design.

Experiment 2: Exploring the neural processing of natural textures in the human somatosensory cortex

Abstract

Evidence has been brought about cortical identification of vibrotactile contrasts. Indeed, these contrasts exist, despite high properties similarities, in all the different textures to which we have a contact. The neural categorization of different vibrotactile contrast in humans is unclear, probably also due to the lack of methods to objectively detect these responses. To overcome this issue, we tested the same novel use of the frequency-tagging approach allowing contrast-specific neural responses to be tracked based on their expected frequencies. But this time, we wanted to test a new method to deliver vibrotactile stimulation to the human skin. We used a passive tactile stimulation by Stimtac robot-related platform which delivers vibrotactile stimulus on a stationary fingertip with constant force and velocity, thus simulating by a more realistic natural texture exploration. The EEG was recorded while participants received 32 s sequences of vibrations presented at 2.5 Hz. A natural texture simulation contrast was embedded every fourth textural item (AAAB or BBBA), such that a response observed in the EEG at exactly $2.5 \text{ Hz}/4$ (0.625 Hz) or harmonics should be the signature of distinct discrimination and generalization elements processing. Contrast-related responses were not identified in any case. We project to review the technical means of our experiment to ameliorate the accuracy of responses detection. Overall, this new combination of frequency-tagging with an oddball design does not provide here a priori objective evidence on the neural processing of natural textures but this is, to our belief, at first probably due to other biases. These biases may be essentially due to the new method tested and its mounting.

Introduction

Goal of project: Importantly, the tactile textures we face in everyday life have highly similar physical properties (overlapping spectral content of vibration). Yet, despite this high similarity, these surfaces are discriminated as distinct textures by the human brain. In addition, when the fingertip explores a given surface several times, the vibrotactile input gathered in each exploration is unique and different from the other explorations of the same surface. Yet, despite this high variability, the vibrotactile inputs gathered from the different explorations are recognized as coming from the same surface by the human brain. Here, the study seeks to understand the neural mechanisms underlying this perceptual categorization, i.e., the capacity of the human brain to discriminate and generalize across a large variety of tactile inputs. The

question is addressed using natural tactile textures explored by the index fingertip of the right hand and electroencephalography (EEG) in healthy participants.

State of the art: Perception of textures through touch is essentially a dynamic exploration process, involving movement of the fingers such as repetitive stroking of a surface to explore its texture. It is by sliding on a texture that a fingertip facilitates the categorization of highly similar textures (Hollins et al., 2000²⁶; Srinivasan et al., 1990²⁷; Morley et al.; 1983²⁸). Yet, most studies treating about touch perception have focused on the brain responses elicited by static stimuli such as static skin indentation, or the neural responses elicited by dynamic but artificial stimuli (McGlone et al., 2002²⁹). A Mougou et al. 2016³⁰ study suggests than a novel means to explore the cortical processing of sensory information generated by the dynamic tactile exploration of natural textures in humans. This is to tag the cortical activity related to the processing of complex skin vibrations due to textured surface fingertip exploration by periodically modulating the amplitude of texture exploration-induced vibrations such as to record a steady-state evoked potential (SS-EP). This way, the stimulatory sequences call by a less artificial manner natural textures exploration. The instrument used is a Stimtac platform³¹ placed on a robot which allows the vibrating platform to be slipped against the fingertip of the right hand with a relatively constant force and velocity while keeping the fingertip stationary (passive tactile stimulation). This means is taken back in our Experiment 2 to understand the neural processing of natural textures. Furthermore, to relate this 2nd experiment to Experiment 1, we retain a Zainos et al. study on monkeys published in 1997³² concerning central categorization. In the study, two monkeys are trained to categorize the speed of moving tactile stimulus. The conclusion reports that the primary somatosensory cortex (S1) is involved in the extraction of higher-order perceptual features, thus playing a potential role in the perceptual categorization of tactile information in S1. This hypothesis is corroborated by our first EEG study (Experiment 1) having identified neural activities originating from S1 related to the discrimination of complex tactile textures. As in experiment 1, our study here is based on a specific experimental method originally developed to investigate with EEG frequency-tagging the neural mechanisms of perceptual categorization of faces in humans (Rossion et al. 2015¹¹). Based on these results, the present study aims to extend the investigation to more ecologically valid, hence more variable, tactile textures.

Reason of interest: Our general goal is to understand tactile information processing. This experiment tends to elucidate the neural mechanisms underlying the perceptual categorization of natural textures exploration in humans. Psychophysics studies posit that two components of high-level perception are involved in categorizing vibrotactile information: generalization and discrimination (Rossion et al., 2015¹¹). Here, we test the neural responses related to

generalization and discrimination in vibrotactile texture perception. This experiment is thus structured so that these two components may be separately underscored. The method used to investigate these processes is EEG frequency-tagging, which allows the identification of brain responses specific to vibrotactile stimulations sets and specific to the processing of tactile contrast based on the expected frequencies of this contrast determined by the structure of the vibrotactile stimulation.

Experiment: Simulated natural textures exploration by right index

Participants: 8 participants between 16 and 50 years old without neurological and/or psychiatric disorders have been recruited for this experiment. All the data were interpretable. There were no participant's data rejection.

Vibrotactile stimulus: The stimulus consists of four sequences of 32 seconds each of continuous vibrotactile inputs. The vibration is transmitted via the same vibrating Stimtac platform placed on a robot used in Mougou's et al. study³⁰. These sequences are composed of a series of different vibration signals of 200 ms duration transmitted by the Stimtac platform, embedded in 400 ms displacement of the Stimtac platform against the fingertip by the robot (figure 7). The vibration signals transmitted by the Stimtac platform correspond to fluctuations of tangential force occurring at the index fingertip during ten explorations of two different tactile surfaces A and B (consisting in two different metal meshes) at constant velocity, measured using a tribometer. Hence, although the vibrotactile stimulation is passive, the use of these vibratory signals and their transmission through the Stimtac apparatus coupled with the moving robot aims to simulate the vibrotactile sensation elicited when actively exploring each of the two surfaces ten times.

In the first sequence s1, the signals corresponding to the explorations of the surface A are presented continuously in randomly permuted order. In the second sequence s2, the signals corresponding to the explorations of the surface B are presented continuously in randomly permuted order. In the third sequence s3, the signals are delivered according to an AAAAB pattern, where A corresponds to the different explorations of the surface A, and B corresponds to the different explorations of the surface B. In the fourth sequence s4, the signals are delivered according to a BBBBA pattern.

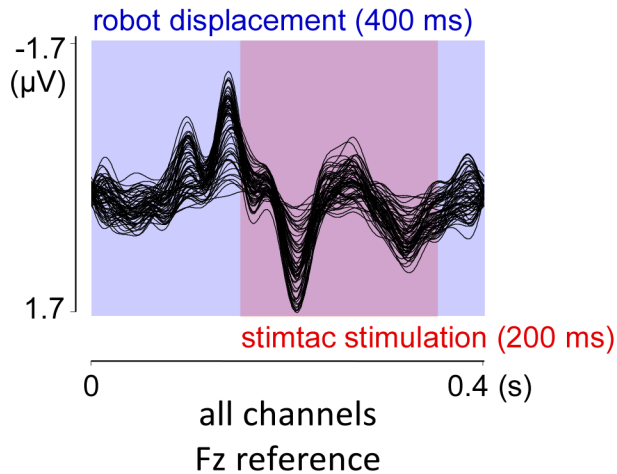


Figure 7. Time course of the EEG response to the tactile stimulation in the four sequences, from the beginning to the end of the robot displacement, including the vibrotactile stimulation via the Stimtac platform (each line corresponds to each EEG channel). There is a clear EEG response to the tactile stimulation, characterized by multiple positive and negative deflections of the EEG signal.

Experimental conditions: Each vibrotactile sequence is sent to the right index. 2 experimental blocks are established. The first includes s1 and s2. The second includes s3 and s4. The different blocks are applied in counterbalanced order across participants. In each block, the sequences are applied in counterbalanced order across participants. Each block consists in 5 consecutive repetitions of each sequence. During all stimulations, the participant is subjected to listening to white noise in order to avoid biasing the results by auditory perception of the stimulus. For optimum participants' attention, they are asked to properly focus on the stimulus. At the end of each trial, the participants must report any variation in rhythm, intensity and/or texture in the sequence and describe the perceived vibration. The participants are not allowed to look at the platform moving at each trial. This is to avoid that a visual activity be elicited at the frequency of displacement of the platform, thus overlapping with the vibrotactile activity.

Expected observations: As in Experiment 1, the experiment design may benefit of the advantages of the frequency-tagging approach with an oddball paradigm. The analysis is based on the EEG responses spectrum in parallel with topographical representation of the responses. First, as each signal is embedded in a robot displacement of 400 ms duration against the fingertip, we expect to find EEG responses aligned to the tactile stimulation elicited by the robot displacement and the vibrotactile texture every 400 ms, i.e. at a frequency of 2.5 Hz (f_{pr}). However, in sequences s3 and s4, we also expect to find additional EEG responses aligned to the contrast of tactile texture presented according to the AAAAB or BBBBA pattern every 4 x 400 ms = 1600 ms, i.e. at a frequency of 0.625 Hz (f_B). An EEG response at this frequency would thus demonstrate the capacity of the human brain to discriminate across two different

tactile textures despite their highly similar physical properties, and to generalize across different explorations of the same texture despite their high variability. We believe that the vibrotactile information processing takes place in S1 after looking on Experiment 1 results. We expect the projection of cortical brain responses for stimulation of the hand to appear on electrodes contralateral to the stimulated hand (parietal area). The reference electrode is always the virtual average of the recording electrodes.

EEG recording and processing: Same as in Experiment 1, except that the EEG processing stages are performed by the Letswave6 function created for MATLAB and that the epochs, lasting 32 s, are obtained by segmenting the recordings from 0 to 32 s relative to the onset of the vibrotactile stimulus.

Results: During the experiment, participants subjectively describe what they feel after each stimulation. The 4 sequences (s1, s2, s3 and s4) are most often reported as granular surfaces, rarely as smooth surfaces. The plate back and forth movements are identified by all the participants. The contrast variation rhythms at 0.625 Hz (f_B) are never identified by the participants. In the frequency spectrum, we observe, as expected, a peak at 2.5 Hz corresponding to the f_{pr} , for all experimental conditions (figure 8). We also observe its harmonics: from $2f_{pr} = 5$ Hz till $12f_{pr} = 30$ Hz. However, no peak at 0.625 Hz corresponding to the f_B is observed in the 4 sequences. Other peaks are observed in the 4 sequences at 1.25 Hz and its multiples till 30 Hz. Although this set of peaks matches with the harmonics of $f_B = 0.625$ Hz, it might also be due to the back and forth movements of the metal plate. One back and forth movement lasts 800 ms which corresponds to a frequency of 1.25 Hz. Finally, the contralateral topography of this activity is compatible with neural processing of tactile information by somatosensory cortical areas such as S1 or S2. But it is not specific to the somatotopic organization of S1 (this would require testing the foot as well, as done in the previous experiment).

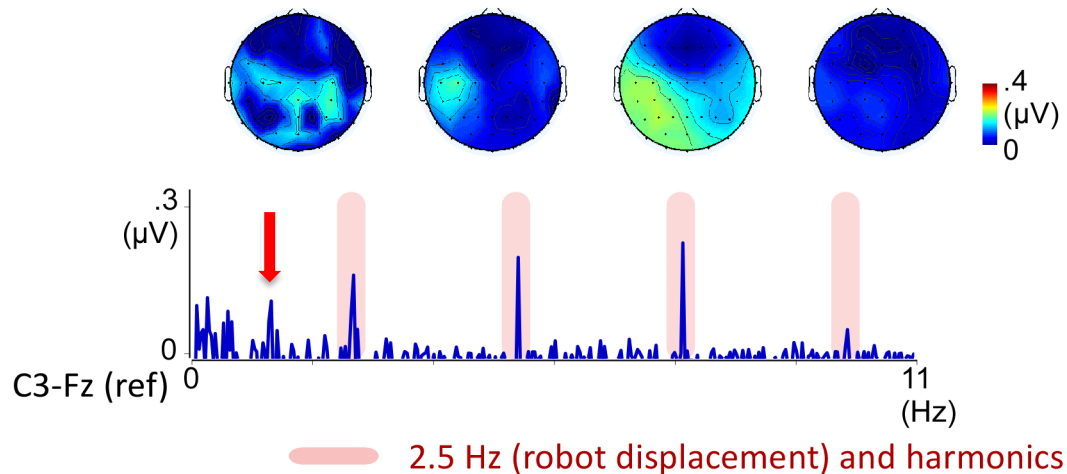


Figure 8. EEG frequency spectrum (centro-lateral EEG channel C3). There is a clear response at 2.5 Hz and harmonics, corresponding to each tactile stimulation in the sequences, with a contralateral topography compatible with S1 or S2 sources. However, there is no significant response at 2.5 Hz/4 corresponding to the discrimination across the two tactile textures. The red arrow points to the 1.25 Hz pronounced peak, thus signifying the brain activity related to the periodic movement of the plate.

Statistical confirmation: See Nozaradan et al., in prep.

Discussion

Interpretation of the results: There is a brain response to the sequence of displacement of the platform and of vibrotactile stimulus, revealed by the peaks at f_{pr} and harmonics in the frequency spectrum of the four sequences, especially s1 and s2. Observing peaks at the frequency of displacement of the plate does not provide any information on the ability of the system to generalize natural textures of the same category. Indeed, this response could simply be a low-level tactile response to the skin deformation occurring every time the plate moves. We can better apprehend generalization by scrolling a same texture at different speeds. That there are no peaks at 0.625 Hz and harmonics in s3 and s4 frequency spectra does not necessarily mean that there is no discrimination for vibrotactile information neural processing. A first explanation at first glance may be the concealment of the $f_B = 0.625$ Hz peak in an excessive background noise. Another explanation for this observation may be more general. It may refer to a theoretical issue, for example that there is simply no neuro-encoding of such information. A problem with the design like an insufficient vibro-stimulation intensity so that the threshold required for discrimination of two different natural textures is not exceeded could be another reason. In this connection, it is important to point out the 1.25 Hz bias. 1.25 Hz may be at the same time the fundamental of one back and forth movement of the Stintac metal plate and the first harmonic $2f_B$ of an eventual $f_B = 0.625$ Hz peak. At the same time, peaks at the multiples of 1.25 Hz may be simultaneously the harmonics of both elements. To avoid such

bias, it would be suitable to repeat the experiment using another material, haptuators for instance. But the hypothetical advantage of using the Stimtac and robot was to elicit vibrotactile stimulation imitating natural textures. Vibrotactile textures generally occur when there is a relative displacement of a surface against the skin (the displacement of the plate imitating the natural passive displacement of a texture against the skin of fingers). But this inherent characteristic of vibrotactile texture cannot be achieved by haptuators which are fixed on the skin. Instead, we can also use an AAAAB structure, such that the frequency of each displacement of the platform does not overlap with the frequency of the contrast in tactile texture.

General conclusion: The experiment does not allow us to highlight completely the perceptual categorization mechanisms of natural tactile textures. This does not mean, perforce, that there is no perceptual categorization nor that the original concept is wrong. According to the possible reasons explaining such unexpected observations, we plan to revisit our experiments designs hoping to come across significant responses. To gain in precision, we consider repeating these experiences by doing intracranial EEG recordings in patients undergoing an intracranial EEG recording for the diagnosis and treatment of intractable epilepsy, which provides a better spatial resolution as compared to scalp EEG. In the same way, we still don't know how natural textures are spatially represented in brain, which is a horizon to explore in the same domain.

Experiment 3: Exploring the spatial representations of natural textures in the human somatosensory cortex

Abstract

The exploration of textures goes through the spatial representation that we have of them. Knowing that vibrotactile contrasts processing takes place in S1 thanks to Experiment 1, it may be intriguing to discover the neural mechanism of spatial representations of natural textures. The fact remains that other sensory areas, as visual and auditory cortex, pass by a difference calculation mode rather than a converging mapping procedure to treat spatial representation of their respective information. This mode of convergence may depend of the spatial distance between the simultaneous stimuli. To highlight this mechanism, we tested again the frequency-tagging approach allowing contrast-specific neural responses to be tracked based on their expected frequencies. The EEG was recorded while participants received 32 s sequences of vibrations presented at 5 Hz. A spatial texture contrast created by spatially-distributed tactile scenes was embedded every fourth textural item (AAAB), such that a response observed in the EEG at exactly $5 \text{ Hz}/4$ (1.25 Hz) or harmonics should be the signature of spatial contrast processing. Moreover, to emphasize the difference calculation mode vs. convergence of maps, we expected variety in the amplitude of the responses across the different experimental conditions which were sequences of white noises all different from each other transmitted by two haptuators to simultaneously stimulate two parts of the body. But contrast-related responses were not identified in any case, as in Experiment 2. We project to augment the number of participants in the hope of extricating statistically valuable peaks. Overall, this frequency-tagging combined to the oddball design does not provide a priori objective evidence on the neural processing of spatial representations of natural textures, but this might probably be encountered by the adjustment of some experimental elements.

Introduction

Goal of project: Understand the cortical encoding of vibrotactile inputs by investigating the integration and lateral inhibition processes underlying spatially-distributed tactile scene analysis (i.e. somatotopic maps convergence) in the human somatosensory cortex. The research over spatially-distributed tactile scene analysis focuses on demonstrating that the somatotopic maps convergence mode can be modeled as a difference calculation rather than a sum of converging signals.

State of the art: It is known that visual and auditory systems integrate spatially-distributed scenes based on a difference calculation. For example, the central detection of sound

localization in mammals is based on two different means of analyzing acoustic waveforms. While the first means constitutes a spectral analysis in which sound energy provides sound-localization in vertical dimension, the second means by which sound localization is achieved is based on central detection and comparison of differences in the delay between the onset of vibration between the two eardrums. This second means underlies sound spatial representation in the horizontal dimension (Grothe et al., 2010³³). These two systems are sensory systems. We can thus think that the other sensory systems work according to the difference calculation mode of spatially-distributed information processing. The somatosensory system, which is a sense system, can then be approached through this point of view.

Reason of interest: Tactile signals provide direct information about the location of tactile stimuli. However, touch localization seems to be a constructive process in brain. Tactile localization is not bound to one reference frame but always relies on information coded with respect to several reference frames. The result of integrating the potentially conflicting pieces of information determines tactile location estimates (Badde and Heed, 2016³⁴). But this integration process has not been yet elucidated. Inspired by the revealed mechanisms of maps convergence in other sensitive systems, especially visual and auditory systems, we seek to explore the somatotopic maps convergence mechanisms in the human somatosensory cortex by frequency-tagging, demonstrating a difference calculation of maps convergence mode.

Experiment: Spatially-distributed tactile stimulation of the hands

Participants: 14 participants between 16 and 50 years old without neurological and/or psychiatric disorders have been recruited for this experiment. The data of 9 participants were interpretable. However, due to technical problems related to the illegibility of the trigger, the data of the other 5 participants were not able to be analyzed.

Vibrotactile stimulus (figure 9): The stimulus consists of four sequences. The four sequences of 32 s each follow the AAAB pattern. Each A and B item lasts 200 ms and therefore appears at a frequency equal to 5 Hz (f_{pr}). The appearance of the B item is characterized by $f_{pr}/4$, equal to 1.25 Hz (f_B). In the four sequences (s1, s2, s3 and s4), each item is represented by a Gaussian noise (white noise) burst whose bins are shuffled over the sequence (i.e. each item is different from the others). These Gaussian noises mixture sequences are stereo-transduced through two channels: channel-1 and channel-2 of a two-haptuators transmission box. In the first sequence (s1), channels 1 and 2 transmit the same A or B items concomitantly all over the sequence. There is no oddball in this sequence. In the second sequence (s2), channels 1 and 2 transmit the same A items, but the concomitantly transmitted B items are always different between the two channels all over the sequence. The oddball is thus created by the mismatch

between the two different B items transmitted concomitantly to the two channels, interleaved within a sequence where all other items (items A) are matched between the two channels. In the third sequence (s3), channels 1 and 2 transmit different A or B items concomitantly all over the sequence. There is no oddball in this sequence. In the fourth sequence (s4), channels 1 and 2 transmit different A items concomitantly, but the concomitantly transmitted B items are always the same between the two channels all over the sequence. The oddball is thus created by the match between the items B transmitted to the two channels, embedded in a sequence with all other items (items A) do not match between channels 1 and 2. Therefore, these four sequences simulate different spatially-distributed tactile scenes.

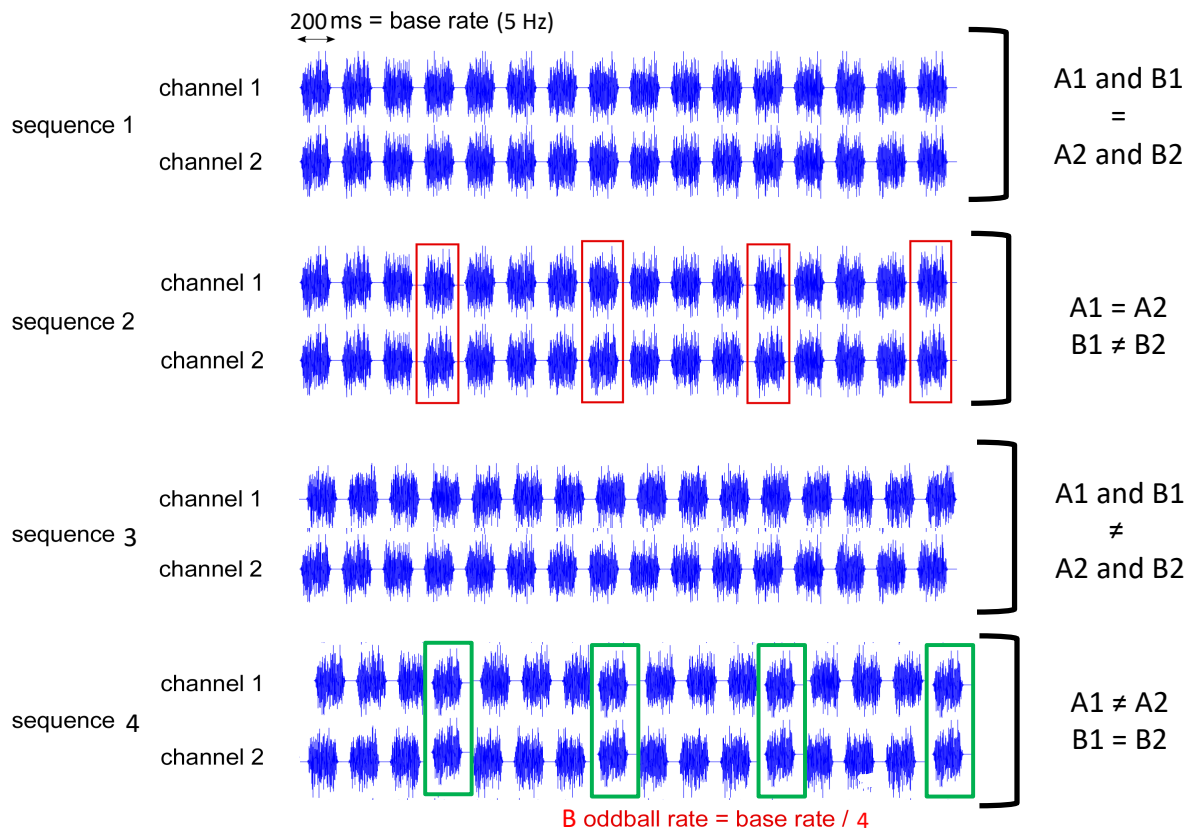


Figure 9. Vibrotactile stimuli. Participants were stimulated with distinct sequences of two repeated vibrotactile stimuli, A and B. These sequences were transmitted by two haptuators corresponding to channels 1 and 2 held between the tips of the index finger and the thumb of left and right hands concomitantly for bilateral condition. They were transmitted by two haptuators corresponding to channels 1 and 2, one stuck between the tips of the index finger and the thumb of the dominant hand and the other on the palm of the dominant hand by the 4th and 5th fingers.

A. Structure of the sequences. Every fourth stimulus, stimuli B were interspersed between stimuli A, and this pattern was repeated during 32 s. The presentation rate (base rate or PR) corresponds to the repetition rate of the vibrotactile stimuli in the sequence (stimulus duration = 200 ms; $f_{PR} = 5$ Hz); the repetition rate of the stimulus B corresponds thus to the fifth of the presentation rate ($f_{PR}/4 = 1.25$ Hz).

B. Representation of the four sequences. In the four sequences, A and B consisted of Gaussian white noises. In condition 1 (sequence 1), channels 1 and 2 transmit exactly the same stimulus concomitantly with no difference between A and B items. In condition 2 (sequence 2), channels 1 and 2 transmit the same A stimulus, but the B stimuli are always different between the two channels thus creating an oddball. In condition 3 (sequence 3), channels 1 and 2 transmit different A or B items concomitantly all over the sequence. In condition 4 (sequence 4), channels 1 and 2 transmit different A stimuli but the same B stimulus thus creating an oddball. These four sequences simulate distinct spatially-distributed tactile scenes. The unilateral vs. bilateral conditions extend the calculation mode study to lateral inhibition process exploration.

Experimental conditions: 2 experimental blocks are established. In the two blocks, the four sequences are played. In the first block, each vibration sequence (s1, s2, s3 and s4) is sent to the right hand (unilateral testing block). The vibration transmission is ensured by 2 haptuators on the right hand. One is stuck between the pulps of thumb and index; the palm maintains the other. In the second block, each vibrotactile sequence is sent concomitantly to both hands (bilateral testing block). The vibration transmission is ensured by 1 haptuator in each hand, stuck between the pulps of thumb, index and middle finger. It is reported that tactile perception is maximum in the hands (Scheibert et al., 2009³⁵), that is why we stimulated hands. In both cases, each haptuator is connected to one of the two stereo-transduction channels (1 or 2). The different blocks are applied in random order to the different participants. For the same block, the stimulatory sequences are applied in random order too among the different participants. Once a block is triggered, each sequence is repeated 6 consecutive times. During all stimulations, the participant is subjected to listening to white noise to avoid biasing the results by auditory perception of the stimulus. For optimum participants' attention, they are asked to properly focus on the stimulus. At the end of each launch, the participants must report any variation in rhythm, intensity and/or texture in the sequence and describe the felt stimulation tone.

Expected observations: The reference electrode is Fz. We expect the appearance of peaks at a frequency equal to the $f_{pr} = 5$ Hz and at its harmonics in the frequency spectrum of the considered electrodes for all the different stimulus sequences applied. For the stimulus sequences s2 and s4, where B items constitute an oddball, we expect the appearance of peaks at a frequency $f_B = 1.25$ Hz and at its harmonics in the frequency spectrum of the considered electrodes. Nevertheless, if the convergence mode is a difference calculation, we expect some more advanced points. First, an ampler response in s3 where all the white noise of A and B items are different between the two channels, compared to s1 where all white noise of A and B items are identical between the two channels. We expect this because of the predictive coding model. According to this model of predictive coding, an event that has been correctly and accurately predicted by the system will evoke a much lower neuronal activity than an event that has not been well predicted (a "surprise"/an oddball), given that this model explains perception

and cerebral activity in the broad sense as the detection of "errors" in relation to predictions of the system (Spratling, 2017³⁶). Second, a bigger oddball response in s2 where the oddball (item B) is a different white noise between the two channels and where the white noises of items A are all the same between the two channels, compared to s4 where the oddball (item B) is evoked by an identical white noise between the two channels and where the white noises of items A are all different between the two channels. Finally, these predictions are also a function of the spatial distance between the haptuators. The differences between the two channels will be preferentially detected unilaterally than bilaterally. The identical signals contrariwise cancel each other unilaterally: there is almost an extinction of the sensation unilaterally, whereas the sensations persist more clearly bilaterally. The extinction of sensation when the two haptuators are close to each other on the same hand vs. when the haptuators are bilateral could be due to some sort of lateral inhibition occurring between adjacent neurons coding for adjacent parts of the body. Lateral inhibition is the phenomenon in which a neuron's response to a stimulus is inhibited by the excitation of a neighboring neuron. This kind of lateral inhibition increases the contrast when stimulation differs between two adjacent parts but reduces the signal of neurons coding for adjacent parts and receiving exactly the same signal (Bakshi and Ghosh, 2017³⁷).

EEG recording and processing: Same as Experiment 2.

Results: During the operations, participants subjectively describe what they feel after each stimulation. The 4 sequences (s1, s2, s3 and s4) are reported as granular surfaces. The contrast variation rhythms at 1.25 Hz (f_B) are never identified by the participants. In the EEG frequency spectrum, we observe, as expected, a peak at 5 Hz corresponding to the f_{pr} , for all experimental conditions. We also observe 3 harmonics: from $2f_{pr} = 10$ Hz, $3f_{pr} = 15$ Hz and $4f_{pr} = 20$ Hz. However, no peak at 1.25 Hz corresponding to the f_B is detectable in the 4 sequences EEG spectra for both blocks (unilateral and bilateral hand stimulation). Although the peak at 10 Hz matches with a $2f_{pr}$ harmonic, it might also be due to alpha band activity. In fact, it is likely to be constituted by both some alpha activity and also harmonic of f_{pr} .

Statistical confirmation: See Nozaradan et al., in prep.

Discussion

Interpretation of the results: There is a brain response to one part of the stimulus, revealed by the peaks at f_{pr} and harmonics on the frequency spectrum of the four sequences. The brain therefore processes, consciously or not, the vibrotactile information correlated fine-grained texture. What interests us more precisely is the somatotopic maps convergence mode of this processing. That there are no peaks at 1.25 Hz and harmonics in s2 and s4 frequency spectra does not necessarily mean that the spatially-distributed tactile scene analysis is not based on a

difference calculation. A first explanation at first glance may be the concealment of the $f_B = 1.25$ Hz peak in an excessive background noise. Another explanation for this observation may be more general. It may refer to a theoretical issue, for example that there is simply no neuro-encoding of such information. A problem with the design like an insufficient vibro-stimulation intensity so that the threshold required for discrimination of two different natural textures is not exceeded could be another reason. Or simpler, spatially-distributed tactile scene analysis somatotopic maps convergence mode is not a difference calculation but the sum of convergence signals. On the other hand, no conclusion about a possible lateral inhibition process can be done because results are not comparable between unilateral block and bilateral block from this point of view. We prefer not to retain an explanation yet, considering that the number of participants is not enough to obtain interesting results and that the experiment must be repeated.

General conclusion: The experiment does not prove yet that spatially-distributed tactile scene analysis somatotopic convergence maps use a difference calculation mode to integrate information and does not highlight a lateral inhibition neural processing. In the same time, it does not mean that the integration operates through the summation of converging signals neither. We consider testing more participants for this experiment. This experiment supports otherwise that vibrotactile tested information processing takes place in S1.

Perspectives: The results obtained, far from being satisfying but not excluding our hypotheses, deserve to be reconsidered. According to the possible explanations given to justify such unexpected observations, we may plan to revisit our experiment design hoping to come across better results. But first, it may be interesting to increase the number of participants thus increasing the chance of educing expected peaks.

Experiment 4: Studying the effect of predictability in the processing of sound contrast in human auditory cortex

Abstract

Since Nozaradan's works (Nozaradan et al. 2011³⁸; Nozaradan 2014³⁹; Nozaradan et al., 2016⁴⁰; Nozaradan et al., 2017¹⁶), the frequency-tagging approach combined to the oddball design allowed better comprehension of sound contrasts processing in auditory cortex. Their studies proved effectively the efficacy of this novel method in the exploration of auditory cortex. We are thus adding to the same study line a new experience that deepens this research based on the same frequency-tagging/oddball approach, in parallel with other sensorial cortices in which we tested it until here, that is, the somatosensory system. Here, we are interested by the predictability phenomenon of sound sequences by human brain. We experiment precisely how temporal predictability of sounds generates or modulates neural expectations processes. The EEG was recorded while participants listened to 40.5 s sequences of sounds presented at 8 Hz. A tone or interaural time contrast was embedded every fifth, sixth, seventh fixed sound (BAAAABAAAABAAAAA), or randomly at the same positions. The responses to tone frequency contrast analysis was made possible by cutting each AB repetition in a way that one B is always followed by 4 A, then by concatenating the cut epochs together to obtain a long sequence again. This way, we artificially made the sequence periodic, to be able to identify the peak corresponding to the processing of the contrast such that a response observed in the EEG frequency spectrum should be the signature of contrast processing by neural populations. Moreover, analysis is approached on the basis of amplitude in order to explain the predictability mechanisms. Non yet detailed results assure the efficiency of the experimental method to infirm our hypotheses, once again widening the field of good performance of frequency-tagging combined to oddball (work in progress).

Introduction

Goal of project: In everyday life, we are constantly confronted with the language of our interlocutor, clung to our piece of music or seized by any other sound of the environment. The common point to all these sound sources lies in the fact that we never listen to one and same sound. What gives a fortiori reason to be to our auditory cortex and its ability to distinguish sounds, it is precisely the existence of this variety in tones. The underlying complexity of the perceptual analysis of these various sounds is reflected, on the one hand, in the perception capacity of this or that sound frequency, but also in the interpretation of the contrast born between two different and consecutive sounds in the brain. Moreover, the human auditory

system has a remarkable ability to detect and anticipate rapid changes in fast and continuous acoustic sequences, as is best illustrated by speech and music. Predictability of sounds is well known to be an archaic reflex to flee danger for example. However, neuronal processing of fast auditory contrast and its predictability remains largely obscure, probably because of the lack of methods for objectively dissociating response components specifically related to the contribution of predictability on contrast processing. Here, the experiment tests the manner by which the human brain expresses the predictability of sounds contrasts. The question is addressed using simulated auditory sequences and electroencephalography (EEG) in non-deaf participants.

State of art: It is quite clear that thanks to memory mechanisms, the brain is able to anticipate auditory sequences by recognizing the beginning of it. A 2009 study by Leaver et al.⁴¹, which deals of cerebral activation during the anticipation of sound sequences, suggests that the very existence of neuronal anticipation shows that the recovery of stored sequences of any type implies a predictive reading of the information to come before the real sensorimotor event. On another hand, a Nozaradan et al. study published in 2017¹⁶ provides objective evidence that the new combination of frequency-tagging with an oddball design as we are doing here can be used to characterize the neural responses specific to contrasts in fast, continuous acoustic sequences. Recently, literature on mismatch negativity (MMN) as EEG neural correlate of contrast processing has been developed. MMN is an event-related potential (ERP) waveform induced by deviant stimuli that occur in a stream of regular auditory stimuli (Zhang et al., 2018⁴²). Using two experiments, this same Nozaradan et al. study demonstrates the neural processing of auditory contrast embedded in fast, continuous sound sequences and the involvement of central mechanisms in processing the contrast in addition to peripheral cochlear integration. Based on these results, the present study aims to extend the investigation in understanding the modulation of this processing by endogenous factors such as anticipation and predictability.

Reason of interest: Our general goal is to understand auditory information processing. This experiment tests specifically the impact of the periodicity of the auditory contrast tone on the neural response to tone contrast. We posit that the predictability of periodicity has a restrictive role in neural response specific to the predicted tone contrast in the auditory cortex (cf. predictive coding). The method used to investigate these processes remains EEG frequency-tagging. Because it does not require an explicit response from the participant, this method could be particularly valuable to probe these processes.

Experiment: Auditive stimulation by various predictability sequences

Participants: 22 participants between 16 and 50 years old without neurological, otological, and/or psychiatric disorders have been recruited for this experiment. The data of only 20 participants have been retained. The data of the 2 other participants made uninterpretable by strong noise perturbation have been rejected.

Auditory stimulus: The stimulus consists of nine distinct auditory sequences. The nine sequences of 40.5 seconds each follow the BA_n pattern ($n \in \{4; 5; 6\}$). Each A and B item lasts 125 ms and therefore appears at a frequency equal to 8 Hz (f_{pr}). The appearance of the B item is characterized by $f_B = f_{pr}/(n+1)$. In the first three sequences (s1, s2 and s3), B is interleaved every 5, 6 and 7 tones in a row as following: BAAAABAAAAABAAAAAA. Therefore, these sequences constitute 3 “fixed” experimental conditions with 3 different tone contrast. In the last six sequences (s4, s5, s6, s7, s8 and s9), B is interleaved either every 5 tones, 6 tones, and 7 tones, with shuffled order of the possible patterns in the sequence (1 oddball/5 tones, 1/6, or 1/7). Therefore, these sequences constitute 3 “jittered” experimental conditions with 3 different tone contrast (3 because two different shuffling across the possible patterns were used to minimize any possible effect of learning of the sequence by the participant over repetition of the sequences: s4 and s5, s6 and s7, and s8 and s9). There are 54 presentations of the oddball tone per sequence (18 repetitions of this fixed pattern) in all the sequences. The carrier frequency of A in all the sequences equals 650 Hz. The carrier frequency of B is equal to the carrier frequency of A + 0.02 semitone (a semitone is the interval between two adjacent notes in a 12-tone scale) in s1, s4 and s5. The carrier frequency of B is equal to the carrier frequency of A + 0.5 semitone in s2, s6 and s7. The carrier frequency of B is equal to the carrier frequency of A + 4 semitones in s3, s8 and s9. We like to precise that there is a single oddball suite initially set by sequence design for each jittered sequence. all participants are exposed to exactly the same sequences. The sequences are pre-established, not created each time differently for each condition and participant, this because coding is easier with fixed sequences. The choice of 3 jittered conditions is moreover purposeful. With 2 jittered conditions only, variability is not much possible (it would be difficult to scramble the tracks so that the sequence become unpredictable). With 4 jittered conditions, there would indeed be a lot of variability in the sequence, but we would need longer sequences to have a sufficient number of each jitter too (if we had 4 different jittered conditions and the 4 jittered had to be repeated 15 times, the sequence would be longer than with 3 jittered conditions).

Experimental conditions: Each auditory sequence is played in both ears simultaneously. 6 experimental blocks are established: the 3 “fixed” conditions and the 3 “jittered” conditions. The different blocks are applied in random order across participants, with the exclusion of

orders consisting of a successive presentation of two or three conditions "fixed", or two or three conditions "jittered" (for example: presentation as block s1 – block s4-s5 – block s2 – block s6-s7 – etc. and never block s1 – block s2 – block s4-s5 – block s6-s7 – etc.). By alternating two different jittered sequences for the same contrast, the risk is reduced that the participant learns or retains the sequence after a few repetitions, despite the jitter and the length of the sequences. Any learning / memorizing effect would be detrimental to the unpredictability of the jittered condition. Within a same block, the stimulatory sequences are applied 6 times successively among the different participants. Once a "fixed" block is triggered, each sequence is repeated 6 consecutive times. Once a "jittered" block is triggered, each of both shuffling sequences of one of the possible patterns is repeated 3 times alternately and never consecutively (for example: s4-s5-s4-s5-s4-s5 for s4-s5 "jittered" block), with first sequence in the block counterbalanced across participants (for example: s6-s7-s6-s7-s6-s7 for participant 1 and s7-s6-s7-s6-s7-s6 for s6-s7 for participant 2). Participants focus their attention to the sequences and are instructed not to move. At the end of each sequence, they are asked:

1. Whether there were only one or two distinct tones repeated over the sequence.
2. If answer to question 1 is two, they are asked whether they had a feeling that an additional, high-pitched sound was played on top of the stream of fast repeated low-pitched tones over the sequence or not.
3. Whether the sequence had the same rhythmic structure as the preceding sequence they heard or not.

Expected observations: We know first that auditory contrast information processing takes place in the primary auditory cortex (Bregman, 1990⁴³). Based on previous behavioral studies on contrast detection and auditory stream segregation (Bregman, 1990⁴³; Van Noorden, 1975⁴⁴), a contrast of 0.02 semitone embedded in a continuous sequence presented at 8 Hz is expected to be undetectable because cochlear channels cannot resolve such a small tone contrast (Moore, 2003⁴⁵). Conversely, 0.5 and 4 semitone contrasts are expected to be detectable. We expect the appearance of peaks at a frequency equal to the $f_{pr} = 8$ Hz and at its harmonics in the frequency spectrum of the considered electrodes for the 0.5 and 4 semitone contrasts sequences (Nozaradan et al., 2017¹⁶). This would confirm the neural response specific to the contrast in fixed and jittered sequences. We expect a more amplified neural response for higher contrast differences, i.e. with 4 semitone contrasts compared to 0.5 semitone contrasts (Nozaradan et al., 2017¹⁶). Furthermore, we expect to detect a less amplified neural signal with the fixed conditions contrasts. This is to demonstrate the impact of the predictability in periodic appearance of listened tones by a mechanism of restriction of neural response.

Brief overview of results: The first results obtained tend statistically-proved to infirm our initial hypothesis over mechanisms of predictability. Specifically, there was no difference in amplitude between the response to contrast elicited in the fixed vs. jittered condition. In other words, there is apparently no modulation by predictability. Based on these preliminary results, we can conclude that the periodic oddball design, by the high predictability inherent to the periodicity of the oddball, does not bias the EEG response towards larger contrast response due to its predictability. Globally, frequency-tagging joined to the oddball design gain again its spurs in this experimentation.

For EEG recording and processing, complete results, statistical confirmation, and conclusion, see Nozaradan et al., in prep. (work in progress).

General conclusion

The frequency-tagging method related to an oddball design gained one's spurs in various studies of exploration of high-level brain encoding mechanisms. The double advantage of this combination allows a high analytical accuracy by increasing the signal-to-noise ratio during the detection of neuro-cortical activation and a direct and objective identification of brain responses based on their expected frequency. In one of the experiments (Experiment 1) focusing on the somatosensory cortex, contrast-related responses were successfully identified for different vibrotactile contrast contrasts as well as fine-grained natural textures contrasts. Despite the lack of spatial resolution of the EEG, this same experiment allowed, thanks to the new tested design, to establish with precision the cortical localization of information processing (in this case S1). This statistically demonstrates that this new combination of frequency-tagging with an oddball design can be used to characterize contrast-specific neuronal responses in vibrotactile sequences. However, the other two vibrotactile stimulus experiments (categorization - Experiment 2 - and spatial representation - Experiment 3 - of natural textures) missed this objective because they did not provide significant results. Several technical and practical justifications have been put forward to explain this lack of results. On the other hand, we cannot avoid saying that this clearly reveals a first drawback of the frequency-tagging / design oddball method. Indeed, when the characteristic frequencies have an undetectable spectral amplitude, an experiment following this specific design is vain despite the increase of the signal-to-noise ratio. Another disadvantage of this combination that we can extricate from the first experiment, is the very interpretation of the tagged oddball frequency. Although this is not directly related to the methodological conception of frequency-tagging, the interpretation of the results may be biased by the confusion between 2 or more possible sources of brain activity (e.g. contrast of frequency vs. contrast of saliency in experience 1). Moreover, the auditory experience launched appears to be strongly in favor of this efficiency, although the concrete results have not yet been described. Not to mention that many other experiments exploring the visual cortex have proven the effectiveness of this new approach.

Finally, it is obvious that despite its advantages, the frequency-tagging of oddball design does not shed all the light on a specific mechanism of cortical processing of a sensory stimulus. It is therefore interesting to compare the precise and objective conclusions of this double combination with the results revealed by other recording techniques than the EEG, for example the fMRI which have a better spatial resolution. But the application of our performant experimental method can even be a great innovation in the field of medical research itself because it does not require an explicit response from the participant, for example to better

understand and treat neurological and psychiatric disorders in particular. Oddball paradigm has additionally proved to be a useful tool in pattern recognition disability as in Parkinson's disease or schizophrenia. It can therefore be a useful task in the education of patients with speech and/or motor disabilities (Siegert et al., 2006⁴⁶; Siegert et al., 2008⁴⁷; Jongsma et al., 2012⁴⁸).

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Author's contribution

My personal contribution to the development of this entire study first required the reading of many scientific articles to familiarize me with the world of neuroscience, in particular sensory cognition, as well as with the usual methods of experimentation (frequency-tagging, oddball design, etc.). The acquired knowledge was quickly put into practice by the fact that I was the purchaser of all the experimental data, with the exception of the very first experimental manipulations of Experiment 1, Part 1, freshly started before my arriving at the laboratory. I also benefited in a practical way from my few years of laboratory to learn how to use software such as MATLAB and Letswave for the processing of complex mathematical data such as an EEG signal.

All the experiments were designed by Sylvie Nozaradan. However, the first experience allowed me to participate intellectually in the conception of the second, more particularly by thinking technical and practical adaptations of the experimental setup. It took us several weeks of thinking with André Mouraux (supervisor) to get to the final technical side of stimulation by Stimtac and robot. Following the disappointment with the results obtained in this experiment and in the following, I participated in the proposal of new experimental manipulation means for these 2 studies that have not yet emerged for reasons of time and of general interest. Indeed, on this last point, the advantage being for my superiors to deepen the conclusive and promising results of other of their studies (Nozaradan et al., 2017¹⁶ for instance), and for me to explore different sensory systems, we supported the idea of returning to the experience 2 and 3 in the future, and further explore the auditory cortex in particular. The interpretation of the results and the study prospects were developed in consultation with Sylvie Nozaradan and André Mouraux.