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Research Report

Distinct neural responses to chord violations: A multiple source analysis study

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ABSTRACT

The human brain is constantly predicting the auditory environment by representing sequential similarities and extracting temporal regularities. It has been proposed that simple auditory regularities are extracted at lower stations of the auditory cortex and more complex ones at other brain regions, such as the prefrontal cortex. Deviations from auditory regularities elicit a family of early negative electric potentials distributed over the frontal regions of the scalp. In this study, we wished to disentangle the brain processes associated with sequential vs. hierarchical auditory regularities in a musical context by studying the event-related potentials (ERPs), the behavioral responses to violations of these regularities, and the localization of the underlying ERP generators using two different source analysis algorithms. To this aim, participants listened to musical cadences constituted by seven chords, each containing either harmonically congruous chords, harmonically incongruous chords, or harmonically congruous but mistuned chords. EEG was recorded and multiple source analysis was performed. Incongruous chords violating the rules of harmony elicited a bilateral ERAN, whereas mistuned chords within chord sequences elicited a right-lateralized MMN. We found that the dominant cortical sources for the ERAN were localized around Broca's area and its right homolog, whereas the MMN generators were localized around the primary auditory cortex. These findings suggest a predominant role of the auditory cortices in detecting sequential scale regularities and the posterior prefrontal cortex in parsing hierarchical regularities in music.

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Abbreviations: ERAN, early right anterior negativity; Sn, Neapolitan subdominant; DD, double dominant chord; T, tonic position; BESA, brain electric source analysis; RS, regional sources; SVC, small volume correction; ROI, region of interest; SPM, statistical parametric mapping

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1. Introduction

The human brain is able to extract regularities and form hierarchical structures from the auditory environment. These regularities may consist of repetitions of one or more features contained in the sounds or in the rules of succession of particular sound features, e.g., the higher the pitch, the louder the sound intensity (Paavilainen et al., 2007). Sometimes the detection of sequential regularities (and the deviations from them) during the course of an experiment may be reinforced by their long-term neural representations existing in the auditory cortex, as in the case of phonemes or musical-scale pitches (Brattico et al., 2006; Näätänen et al., 1997; for a review, see Näätänen et al., 2001). Other kinds of regularities are hierarchically organized, meaning events within those regularities have different weights and roles according to previous knowledge, e.g., music harmony or language syntax (Koelsch and Sammler, 2008).

The brain processing of regularities can be studied with EEG by eliciting their corresponding event-related potentials (ERP): mismatch negativity (MMN) and early right anterior negativity (ERAN). According to Koelsch et al. (2009), the MMN is elicited by a deviant stimulus introduced in a sequence in which an acoustic or local abstract feature is repeated and a local rule is established in the course of the experimental session. The ERAN, on the other hand, is elicited by culturally-biased errors in harmony within a melody, depending on long-term knowledge of a musical culture. However, the MMN is similarly modulated when sounds correspond to previous culturally-biased regularities established by exposure to a certain music or language. Hence, the main difference between the phenomena associated with ERAN and MMN resides in the locality vs. the hierarchical structure of the sound regularities. The way in which the brain deals with these two processes in the musical domain has so far gone largely unrevealed. We believe that music is ideal for the study of the neural processing of these types of regularities. In this study, we aimed at investigating the neural mechanisms responsible for detecting musical-scale pitch and harmony errors within a balanced musical context to determine their brain sources and the relationship between the brain activity and the perception of these errors.

In the past decade, extensive research has focused on the extraction of simple regularities from auditory stimulation by using the mismatch negativity (MMN), a type of even-related potential (ERP) component elicited by a deviant stimulus randomly introduced in a train of repetitive stimuli (Näätänen, 1995; Picton et al., 2000). The MMN is a fronto-central negative potential peaking at around 150–250 ms, occurring at early stages of auditory processing regardless of attention and hypothesized to be important for survival by detecting unexpected events (Näätänen, 1995; Näätänen et al., 2007). It has main sources in the superior temporal gyrus and sometimes with weak additional sources in the right inferior frontal gyrus (Opitz et al., 2002; Rinne et al., 2005; Tse and Penney, 2008) and the inferior parietal lobule (Park et al., 2002). The MMN is suggested to reflect the automatic formation of brief neural models of sequential regularities in the auditory environment that are typically formed in the course of the experimental session by repeating acoustic or abstract features of one or several sounds

(Näätänen et al., 2007; Winkler et al., 1996). For instance, an abstract feature MMN has been elicited by the violation of the rule of ascending sound pairs coupled with increasing loudness (Näätänen et al., 2001; Paavilainen et al., 2001).

Music follows culture-dependent rules that govern the way we perceive and conceive it, with pitch as a central dimension. From the set of all the possible sound pitches, Western tonal music is founded on a small subset of 12 pitches included in the chromatic equal-tempered scale, where the interval between consecutive pitches is a semitone (100 cents). With very few exceptions such as the blue notes of the blues scale, this discrete selection of pitches and their relationship to each other determines the most basic and fundamental rules of Western tonal music, be it classical, jazz, or pop musical genres. The rules of the equal-tempered scale concern sequential aspects of sound pitches as they can be extracted by comparing the pitch of the incoming sound with that of the immediately preceding one, with a human sensitivity to pitch deviations of 10–30 cents (Krumhansl, 2000; Lehmann, 2008). Violations of these scale rules in unfamiliar melodies also elicit an MMN-like response with main generators in the non-primary auditory cortex (Brattico et al., 2006). These findings suggest that the MMN is also elicited by violations of musical regularities that are stored in long-term memory rather than only those formed during the course of the experimental session.

Most pieces in Western tonal music are based on smaller subsets from the chromatic scale, e.g., the diatonic scales, which define the hierarchical relations between sounds by means of the rules of tonality. However, when several sounds are played simultaneously creating musical chords, harmony rules determine their relationship instead and are simultaneously influenced by the rules of voice leading (Grove and Colles, 1944). The rules of harmony also determine the order and structural importance of the harmonic events within a musical sequence, thus determining a hierarchical structure within the musical piece. Chord progressions (harmonic progressions) such as the authentic cadence (tonic–subdominant–dominant–tonic) are common representative examples of a hierarchical structure and have been recognized as main carriers of harmony in Western tonal music theory (Piston, 1941).

Violations of the harmonic structure of a musical sequence elicit an ERP component called early right anterior negativity (ERAN), which occurs at 150–250 ms after stimulus onset over anterior regions of the scalp and tends to be right lateralized (Koelsch et al., 1999; Koelsch et al., 2000; Leino et al., 2007). The amplitude of the ERAN is modulated by attention, decreasing as the attention increases and vice versa. Therefore, most studies present a semi-attentive paradigm (Koelsch et al., 2000; Koelsch et al., 2002b; Loui et al., 2005), where the participant listens to the music while performing a task unrelated to the harmony manipulation of interest. In musical experts, the ERAN amplitude is higher than in novices (Koelsch et al., 2002a). The ERAN is elicited specifically by the incongruity of harmonically unexpected events in musical sequences, e.g., by Neapolitan subdominant (Sn) or double dominant chords (DD), at the tonic (T) position (Koelsch and Sammler, 2008; Koelsch, 2009; Leino et al., 2007; Loui et al., 2005; Maess et al., 2001).

The similarities and differences of the ERAN and the MMN have been thoroughly reviewed in Koelsch et al. (2009). These two

electrophysiological brain responses share similar temporal and scalp distributions, with amplitudes increasing with the degree of (acoustic or harmony) violation and both are linked to behavioral discrimination performance (Koelsch et al., 2001). Although the MMN seems to be more strictly automatic as it can be elicited in participants under deep sedation by anesthesia, both the MMN and the ERAN can be elicited pre-attentively (Heinke et al., 2004; Koelsch et al., 2006). In contrast to the MMN, the ERAN has peak latency and amplitude that specifically depends on the degree of harmonic appropriateness (Koelsch et al., 2001; Leino et al., 2007; Steinbeis et al., 2006), which, in turn, is related to prior (implicit or explicit) knowledge of Western tonal harmony. Koelsch et al. (2009) suggested that the MMN relies on short-term memory to compare an event with an immediate prior event, whereas the ERAN relies on long-term memory to compare an event with knowledge derived from prior long-term exposure. However, the MMN is elicited even by violations of the sequential rules of the equal-tempered musical scale, such as mistuning of a pitch in a melody or in a chord (Brattico et al., 2001; Brattico et al., 2006; Brattico et al., 2009; Koelsch et al., 1999) and by changes in the local regularities of phonology (Shestakova et al., 2002). These findings suggest that the MMN is not simply a measure of formation and violation of sensory memory traces but can also be modulated by long-term representations of certain kinds of musical rules already at the level of the auditory cortex.

Previous findings tentatively indicate that the processing of the auditory violations tackled by MMN and ERAN takes place in different scalp locations. Using magnetoencephalography (MEG), Maess et al. (2001) localized the sources of the magnetic ERAN response in pars opercularis of the Broca's area (BA44) and its right hemispheric homolog, with a non-significant tendency towards a right-hemispheric superiority. While some studies support this bilateral localization, calling the component simply early anterior negativity (EAN) (Leino et al., 2007; Loui et al., 2005), others provide evidence for a right-lateralized ERAN (Koelsch et al., 2000; Koelsch et al., 2001; Koelsch et al., 2002b; Koelsch, 2005).

Leino et al. (2007) made a direct comparison between the ERAN and the MMN using deviant chords embedded in the same harmonic context. Three types of sequences consisting of seven chords each were presented: a harmonically congruous sequence adapted from the authentic cadence; a harmonically incongruous sequence that had a Neapolitan subdominant (Sn) chord in the 3, 5, or 7 positions; and a harmonically congruous sequence that had a mistuned fifth note within the chords in positions 3, 5, or 7. Their results suggested that the harmonically incongruous chords elicited an ERAN, with an amplitude that was affected by the harmonic hierarchy of the sequence, as it was larger when the chord succession was less expected (when the Sn was placed instead of the tonic chord, following a dominant chord) than when it was more expected (as when the Sn was placed instead of the subdominant chord, following a tonic chord). On the other hand, mistuned chords elicited an MMN, with an amplitude that was not affected by the position of the mistuned chord in the sequence.

What remains unclear from other studies is how harmony and musical-scale pitch violations are consciously perceived, their relation to the neural activity, and if their underlying processing differs when presented in a similar musical context.

Koelsch et al. (2009) do not explicitly inform about the relationship between serial and hierarchical processing, an important relationship described in language literature (Bahlmann et al., 2008). Furthermore, this review uses data of paradigms in which the two brain responses were elicited by unmatched sound contexts, which alone could explain the differences in the neural findings. Furthermore, the similarities and differences between language and music processing are still being debated. Therefore, there is a need to study these types of violation in a similar musical context and to determine their corresponding neural correlates when elicited in a similar context.

In this study, we hypothesize that the MMN indexes sequential regularities and the ERAN indexes processing of hierarchical sound structure. For this, we wished to determine the relationship between the ERAN and MMN with subjective perception of tuning and harmonic violations. We also wanted to further investigate the results from Leino et al. (2007) by identifying the brain processes associated with the representation of the two types of musical regularities presented in a comparable context, such as chord progressions, using EEG. Furthermore, we wished to determine the cortical sources generating those brain responses by means of discrete source analysis using the software BESA (Brain Electric Source analysis; Grandori et al., 1990; Scherg, 1984; Scherg and Von Cramon, 1986; Scherg and Berg, 1991; Scherg and Picton, 1991; Scherg, 1994) and distributed source analysis with the software SMP 8 (Statistical Parametric Mapping software; Kiebel and Friston, 2004a; Kiebel and Friston, 2004b).

To these aims, we adopted the paradigm of Leino et al. (2007) in which different kinds of musical violations are embedded in the same context, presenting 7-chord cadences with harmonically incongruous Neapolitan chords as well as mistuned chords (see Fig. 1). For the behavioral part of the study, we asked the participants to rate the chord cadences for valence (1=unpleasant to 5=pleasant) and fittingness (1=does not fit to 5=fits). Based on behavioral ratings of emotionality and tension obtained by Steinbeis et al. (2006) and of relatedness obtained by Tillmann and Lebrun-Guillaud (2006) with similar chord sequence material, we expected higher pleasantness and fittingness for musical sequences with a harmonically incongruous chord in the 5th position than the 3rd or 7th positions and similar pleasantness and fittingness for the mistuned chord in all 3 positions within the chord cadences, related to the ERPs' amplitude. Furthermore, we hypothesized that the mistuned chord, representing a violation of the chromatic musical scale, would elicit an MMN with predominant neural sources in the superior temporal gyrus, whereas the Neapolitan chord, violating the hierarchical rules of chord successions, was expected to elicit an ERAN originating in the inferior frontal gyrus (Brattico et al., 2006; Leino et al., 2007; Näätänen, 1995; Näätänen et al., 2004; Winkler et al., 1996).

2. Results

2.1. ERP data

Neapolitan subdominants violating the rules of harmony elicited the frontally distributed ERAN component peaking on average at 228 ms post-stimulus (see difference waves,

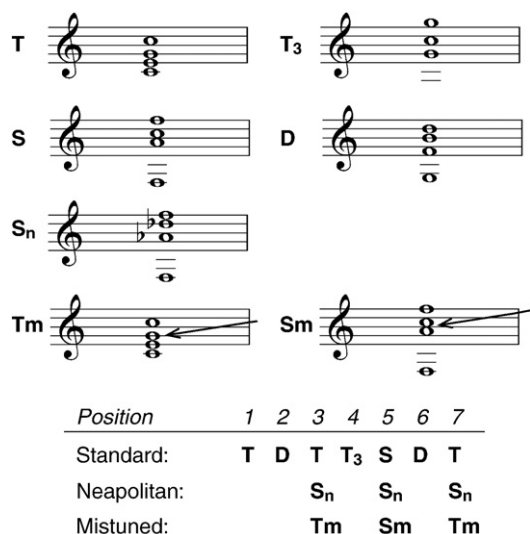


Fig. 1 – Stimuli. T indicates tonic; S, subdominant; Sn, Neapolitan subdominant; m, dominant; T3, inverted tonic; Tm, mistuned tonic; Sm, mistuned subdominant. Top box: Musical notation of the chords used for the stimulus, only in the key of “C” for illustration purposes. The arrows point to the mistuned note in Tm and Sm, respectively. Bottom box: illustration of the musical cadence. The left column shows the type of condition. The right columns show the 7 positions of the cadence and the key deviant chords (3, 5, 7).

The ERAN was most prominent over anterior regions, as reflected by the significant interaction ERP component × distribution: $F_{(1,14)}=6.20, p=.02$, and the contrast comparing the ERAN to the MMN for anterior compared to posterior distribution: $F_{(1,6)}=9.80, p=.02$. We observed overall significant differences in the mean response amplitude between the left and right hemispheres which depended on the type of ERP present, reflected by the interaction ERP component × hemisphere: $F_{(1,14)}=8.01, p=.01$. This resulted from the bilateral distribution of the ERAN and the right-lateralized distribution of the MMN in all the chord positions. Finally, we found a significant interaction ERP component × position × distribution: $F_{(2,28)}=5.17, p=.01$. The contrast showed that the ERAN and the MMN differed in scalp distribution when comparing position 5 to 7: $F_{(1,5)}=23.36, p=.02$. This means that the distribution varied according to the type of ERP and position of the violation. For further testing of these scalp topography differences between ERP components, we conducted discrete and distributed source analyses.

2.2. Discrete source analysis (BESA)

The MMN in the 3 chord positions was modeled with 2 main symmetrical regional sources (RS) originating in the temporal lobe whereas the ERAN in the 3 chord positions was modeled with 2 main symmetrical RS localized anterior to the MMN sources. Other RS were mainly localized to the occipital lobe and most likely caused by alpha waves and non-encephalic noise. The average coordinates of the individually-computed RS models are shown in Table 1. The ERAN RS were localized in BA 44 and BA 45 (Broca’s area and right homolog). The MMN RS were localized in BA 41, corresponding to auditory cortex. These two sources accounted, on average, for >90%–80% of the

Fig. 2). Mistuned chords, violating the rules of the musical-scale tuning, elicited the fronto-centrally distributed MMN peaking on average at 270 ms post-stimulus (see difference waves, Fig. 3).

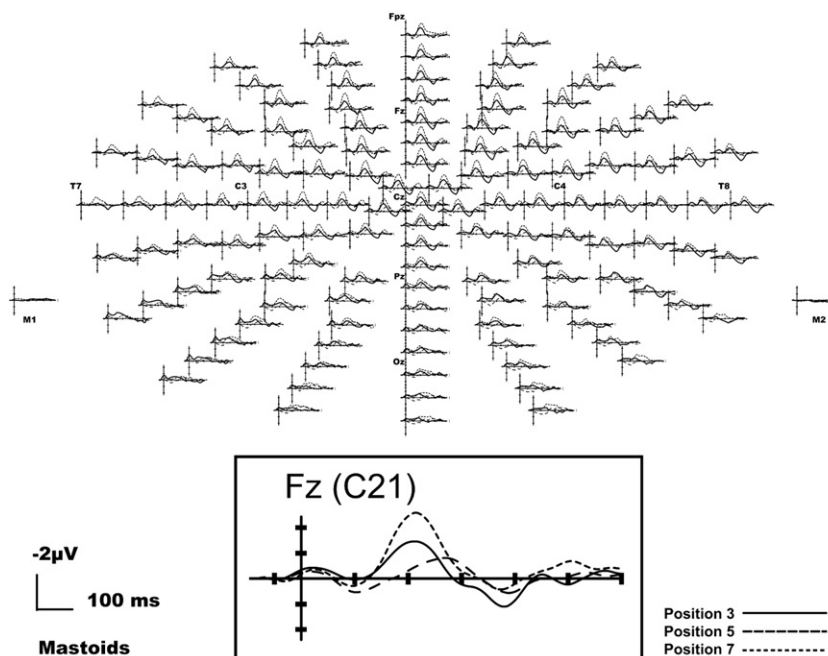


Fig. 2 – Top: top view of the ERP analysis in all 128 electrodes. **Bottom:** difference waves shown in channel 21 (Fz) between ERP responses to harmonically incongruous chords, illustrating the ERAN in the three different cadence positions (3, 5, 7).

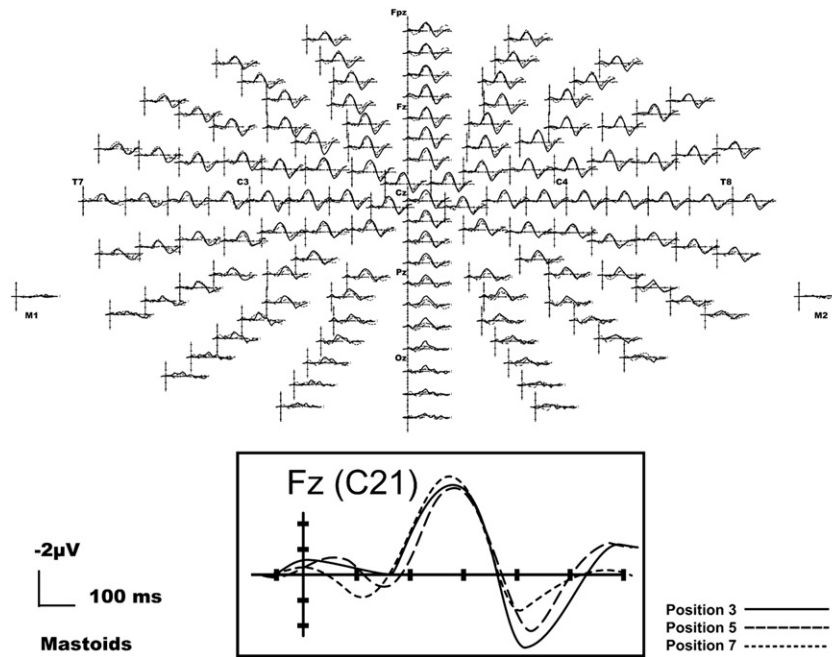


Fig. 3 – Top: top view of the ERP analysis in all 128 electrodes. Bottom: difference waves shown in channel 21 (Fz) between responses to mistuned chords, illustrating the MMN in the three different cadence positions (3, 5, 7).

variance in the data. The rest of the individually-computed RS fitted were not considered for statistical analysis as they explained a negligible amount of variance in the waveforms (<1%–3%). The statistical comparison of the ERAN and MMN individual RS localizations of each participant with repeated-measures ANOVA revealed a significant main effect of the ERP component factor at the y axis, $F_{(1,14)}=59.94$, $p<.001$, due to the ERAN RS being anterior to the MMN RS as shown in Figs. 4 and 5.

2.3. Distributed source analysis (SPM8)

In the small volume correction (SVC) of the ROIs, the MMN showed significant activation in the STG (left hemisphere (L): BA 22; right hemisphere (R): BA 41 and BA 42), whereas the ERAN showed significant activation in the IFG (L: BA 44, BA 45, BA 47; R: BA 44, BA 45, BA 47) with $p<.001$ (see Table 2 and Fig. 5).

Table 1 – Regional sources

| x | y | z | Location |
|------|-----|----|----------|
| MMN | | | |
| -36 | -15 | 19 | STG |
| 36 | -15 | 19 | STG |
| ERAN | | | |
| -37 | 15 | 24 | IFG |
| 37 | 15 | 24 | IFG |

Mean average coordinates of the MMN and the ERAN regional sources in the discrete source analysis. The coordinates are in Talairach space. STG indicates superior temporal gyrus; IFG, inferior frontal gyrus.

2.4. Behavioral data

As visible in Fig. 6, the ERAN5 is consistently the most pleasant and fitting position among the ERAN conditions, whereas MMN3 is the most pleasant and fitting position among the MMN conditions. Statistical non-parametric tests confirmed that the ratings of pleasantness of the chords differed significantly according to their positions in the cadence. For the harmonically incongruous chords: $X^2(2)=6.506$, $p=.03$; for the mistuned chords: $X^2(2)=8.222$, $p=.01$. In the pairwise comparisons, we found significant differences between ERAN5 vs. ERAN7: $T=45.5$, $r=-.38$ (T ="smaller sum of ranks," r ="effect size"), meaning ERAN5 was rated more pleasant than the ERAN7, and between MMN7 vs. both MMN3 and MMN5: $T=23.5$, $r=-.42$; $T=38$, $r=-.36$, respectively, meaning MMN7 was rated as the least pleasant as compared with MMN3 and MMN5. Importantly, ERAN3 did not significantly differ in unpleasantness from ERAN7 ($T=66.5$, $r=-.31$). As for the ratings of fittingness, the position in the cadence had near significant effect on harmonically incongruous chords ($X^2(2)=5.302$, $p=.07$), whereas it was significant for mistuned chords ($X^2(2)=9.791$, $p<.001$). However, there was only one significant difference in the pairwise comparisons between MMN3 and MMN7 ($T=26$, $r=-.47$), meaning MMN7 was rated as the least fitting.

3. Discussion

The present study was conducted to determine the relationship between the ERAN and the MMN with subjective perception of tuning and harmonic violations, the brain processes related to the neural representation of two different

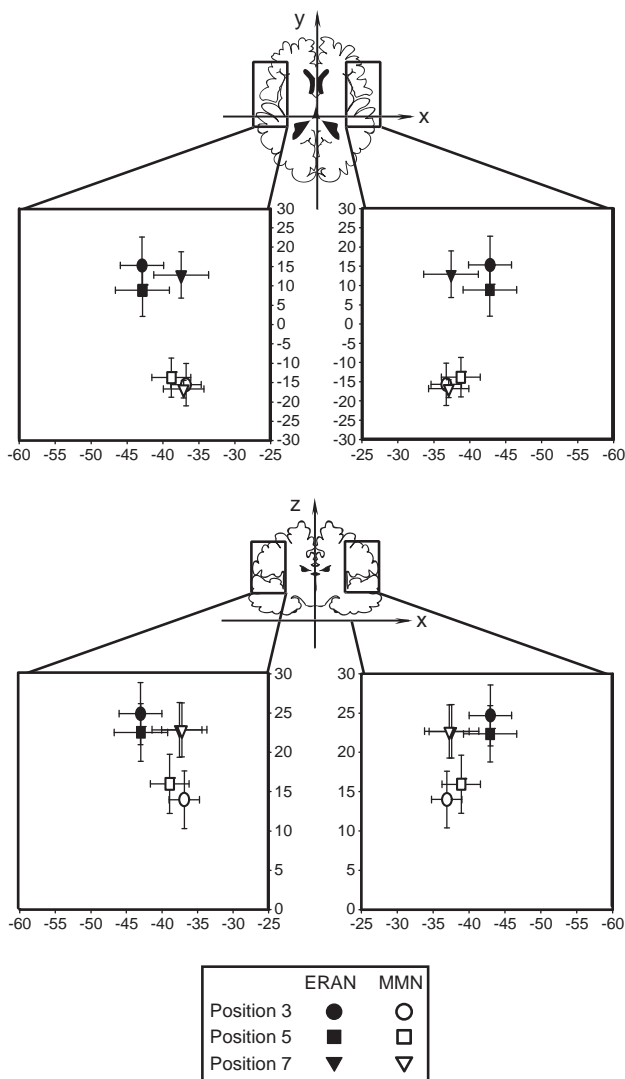


Fig. 4 – Mean location of the regional sources (RS) of all participants in the Cartesian plane. Here, we show the RS separately for condition (ERAN, MMN) and position (3, 5, 7). Top image illustrates the coordinates in the y (anterior–posterior) and x (right–left) axes. Bottom image illustrates the coordinates in the z (top–bottom) and x axes. Left coordinates represent the left hemisphere, while right coordinates represent the right hemisphere. The sources were symmetrically constrained; therefore, hemisphere representation is irrelevant.

kinds of musical regularities and their underlying cortical generators. We found that violations from harmonic regularities, i.e., Neapolitan subdominants replacing the expected tonal chords at the ending of a cadence, elicited an ERAN at around 228 ms with an amplitude that was modulated by the degree of violation of the rules of harmony. Mistuned chords violating the rules of the musical scale elicited an MMN at around 270 ms with an amplitude that did not differ according to chord context. The reason for the early peak latency of the ERAN is that it reflects long-term memory detection of the auditory violations. In contrast, the detection of local auditory violations reflected by the MMN is more computationally demanding and, therefore, slower (Koelsch, 2009). Although

the MMN is also elicited by violations of musical regularities that are stored in long-term memory, it is important to note that the sound regularities that can be formed within an experimental session or that are stored in long-term memory representations, possibly in auditory cortical loci, are local and sequential as they are characterized by specific ratios between neighboring sounds (Brattico et al., 2001; Brattico et al., 2006; Shestakova et al., 2002). In our study, the source analyses based on both discrete and distributed algorithms gave comparable localization results, with the MMN consistently localized around the auditory cortices and the ERAN generated from Broca's area and its right hemisphere homolog, even though the chord incongruities giving rise to the ERAN and the MMN occurred in identical contexts. Moreover, the ERAN was bilaterally distributed whereas the MMN was slightly lateralized to the right hemisphere.

Koelsch et al. (2001) wished to determine whether the ERAN is an abstract feature MMN or a completely distinct ERP. While playing a video game, participants were presented with musical sequences that included either tone pairs raising (standard) or falling (deviant) in pitch. Their results indicated that the ERAN amplitude was specifically dependent on the degree of harmonic appropriateness, whereas the MMN one was not. However, due to the specific paradigm used in that study, the authors did not decisively determine whether the elicited ERAN amplitude variability was a consequence of the tonality change or of the harmonic relationships in the chord sequences. Moreover, the paradigm did not balance the conditions in terms of the spectral complexity of the context since the ERAN was elicited by chords in a chord context, which have a higher sound density compared to the isolated tone pairs eliciting the MMN. This was later clarified by Leino et al. (2007), who found that the ERAN amplitude modulation resulted from the harmonic relationships within the chord cadence. These two studies suggested that the components are elicited by different musical properties of the chord cadence, i.e., scale vs. harmonic hierarchy. Nevertheless, there are no previous studies that directly compare the MMN and ERAN localizations and cerebral sources against each other within the same musical context. Hence, our results further support this distinction between ERAN and MMN components and contribute to knowledge on their cortical generators. Finally, in our paradigm, mistuning can be detected as a violation of musical-scale sequential rules based on long-term memory. However, it should be noted that the mistuned chord could in principle be detected in isolation as it contains other pitches simultaneously presented that could hint for the pitch classes according to the Western tonal scale system. Thus, the MMN here may be, strictly speaking, a “local” process. Importantly, though, mistuning detection is not a mere sensory process based on the roughness and beating in the chord but rather relies on the presence of memory representations of scale pitch relations (Brattico et al., 2006; Brattico et al., 2009).

The MEG study of Maess et al. (2001) and two fMRI studies by Koelsch et al. (2005) and Tillmann et al. (2003) localized the ERAN neural activity in the frontal lobe (Broca's area and right homolog) and other studies have localized the MMN to pitch changes in the auditory cortices at the supratemporal lobe (e.g., Brattico et al., 2006; Tervaniemi et al., 2006a), with

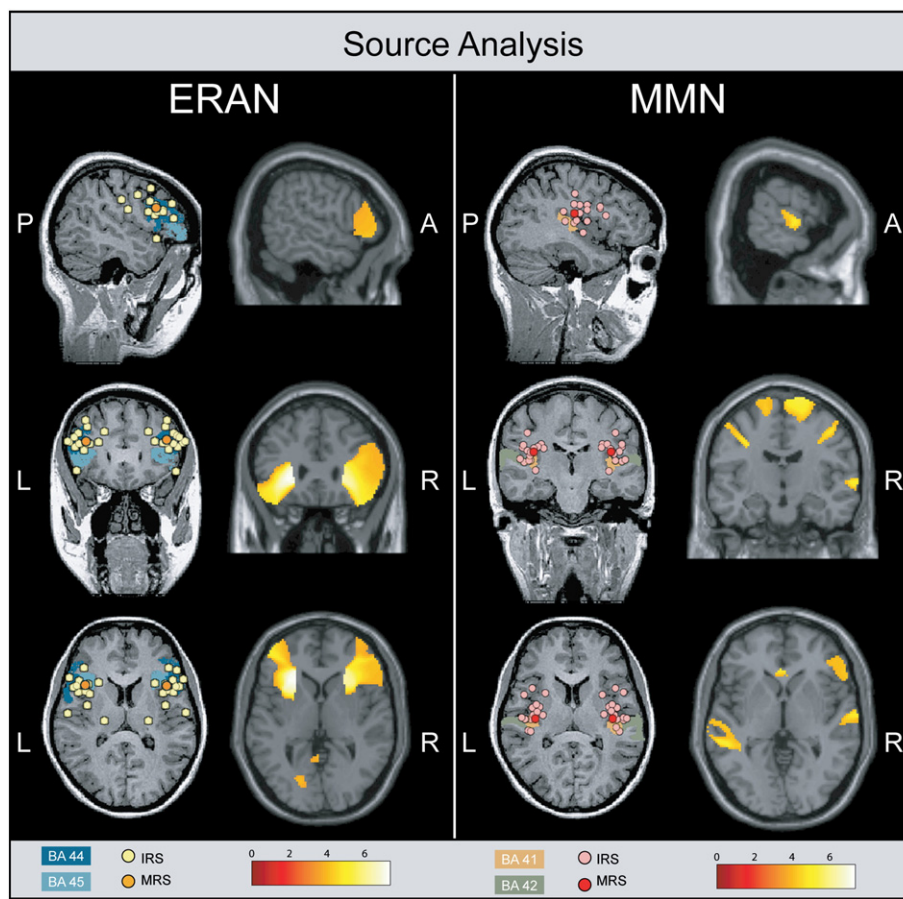


Fig. 5 – The left column corresponds to the ERAN and the right column to the MMN. Inside each column, there are two sub-columns. Left sub-columns: discrete source analysis of the ERAN and MMN responses for all experimental conditions. Right sub-columns: distributed (SPM) analysis of the ERAN and MMN responses for all experimental conditions. The first row shows the sagittal view; the second row shows the coronal view; and the third row shows the transversal view (A indicates anterior; P, posterior; L, left; R, right; IRS, individual regional sources; MRS, mean regional sources). The color bar represents the T-statistic.

additional sources in the right inferior frontal gyrus and inferior parietal lobule (Opitz et al., 2002; Park et al., 2002). In our discrete source analysis, the individual and grand average sources of the ERAN were located significantly more anterior than the MMN sources (see Fig. 4). The average sources of the ERAN were localized around BA 44 and BA 45 in IFG, similar to the study of Maess et al. (2001). The MMN was instead localized in the STG, around BA 41 and BA 42, also consistent with previous ERP and fMRI literature (see Fig. 5). However, we did not find sources in IFG. This may be because our stimuli were not attention catching like the simple acoustic changes used in previous studies as the frontal activation of the MMN has been connected to stimulus salience and triggering of involuntary attention (Deouell, 2007; Naatanen et al., 2010). The SPM source analysis results correspond to the findings in the discrete analysis, strongly suggesting that these ERPs represent different types of processes and that they are likely generated by separated cortical sources.

In the ERP analysis, the MMN was significant in both hemispheres but stronger in the right hemisphere, whereas the ERAN was significant in both hemispheres. This bilateral distribution disagrees with the fundamental nomenclature of

the ERAN that identifies it as right lateralized, with similar temporal and mirrored spatial properties as the early left anterior negativity (LAN) (Friederici et al., 1996; Hahne and Friederici, 2002; Neville et al., 1991). On the other hand, in the present study, the MMN was found to be right-lateralized. Previous studies also obtained a right-hemispheric predominance of the MMN, especially during the detection of non-phonetic auditory stimuli (Brattico et al., 2006; Opitz et al., 2002; Tervaniemi et al., 2000). However, left-lateralization has also been described depending on the non-phonetic feature (Grimm et al., 2006; Tervaniemi et al., 2006b). Furthermore, several studies failed to replicate the right lateralization of the ERAN (Loui et al., 2005; Leino et al., 2007), rather suggesting that this brain response has bilateral generators.

In the behavioral study, we found that the participants consistently rated each cadence differently, indicating that the paradigm successfully examined different musical properties in the same context. Participants expressed higher pleasantness and fittingness for ERAN5 than ERAN3 and ERAN7, whereas MMN3 was rated as the most pleasant and fitting and MMN7 as the least pleasant and fitting. Furthermore, we obtained significant differences of pleasantness between ERAN5 vs. ERAN7 but

Table 2 – Distributed analysis results.

| x | y | z | Z score | P value |
|-------------------------------------|-----|----|---------|---------|
| <i>MMN: superior temporal gyrus</i> | | | | |
| -67 | -17 | 3 | 3.22 | <.001 |
| -55 | -19 | 3 | 3.22 | <.001 |
| -59 | -17 | 3 | 3.19 | <.001 |
| 67 | -12 | 1 | 3.71 | <.001 |
| 51 | -21 | 7 | 3.6 | <.001 |
| 57 | -17 | 5 | 3.52 | <.001 |
| 69 | -19 | 8 | 3.3 | <.001 |
| <i>ERAN: inferior frontal gyrus</i> | | | | |
| -30 | 29 | -3 | 4.65 | <.001 |
| -32 | 20 | 8 | 4.35 | <.001 |
| -32 | 24 | 10 | 4.15 | <.001 |
| -34 | 39 | -4 | 3.73 | <.001 |
| -45 | 43 | -4 | 3.46 | <.001 |
| -38 | 18 | 16 | 3.19 | <.001 |
| 48 | 19 | -3 | 3.38 | <.001 |
| 57 | 19 | -3 | 3.29 | <.001 |
| 63 | 18 | 10 | 3.24 | <.001 |
| 61 | 18 | 6 | 3.2 | <.001 |
| 57 | 20 | 8 | 3.2 | <.001 |
| 32 | 29 | 0 | 4.17 | <.001 |
| 34 | 26 | 8 | 3.84 | <.001 |
| 44 | 44 | -4 | 3.7 | <.001 |
| 38 | 35 | 7 | 3.68 | <.001 |
| 44 | 39 | 2 | 3.59 | <.001 |
| 51 | 43 | 2 | 3.52 | <.001 |
| 46 | 30 | 26 | 3.47 | <.001 |
| 57 | 33 | 9 | 3.3 | <.001 |
| 53 | 29 | 26 | 3.28 | <.001 |
| 62 | 26 | 10 | 3.27 | <.001 |
| 62 | 20 | 6 | 3.25 | <.001 |

Talairach coordinates of the significant peaks localized by the small volume correction (threshold $p < .001$, uncorrected). IFG includes BA 44, 45, and 47, whereas STG includes BA 41 and 42.

not between ERAN3 and ERAN7, contrasting with the MMN results where MMN7 was significantly different than MMN3.

These findings are in accordance to harmony rules that state that a Neapolitan subdominant in the 5th position is harmonically acceptable. On the other hand, the ratings of the cadences containing mistuned chords are in accordance to sequence rules, which state that errors in a sequence increase as the tonality gets more established. However, this is not reflected in increasing amplitude of the MMN according to position. Notably, the pleasantness and fittingness ratings were obtained after the EEG recordings with full attention to the stimuli, whereas the observed MMNs reflect pre-attentive processing, which may account for the slight discrepancy between the behavioral and ERP measures.

3.1. Conclusion

In a direct comparison between the cortical sources of the MMN and the ERAN using a context-balanced paradigm, the present study strongly suggests that the MMN and the ERAN are components reflecting the representation of sequential and hierarchical musical regularities respectively, which have

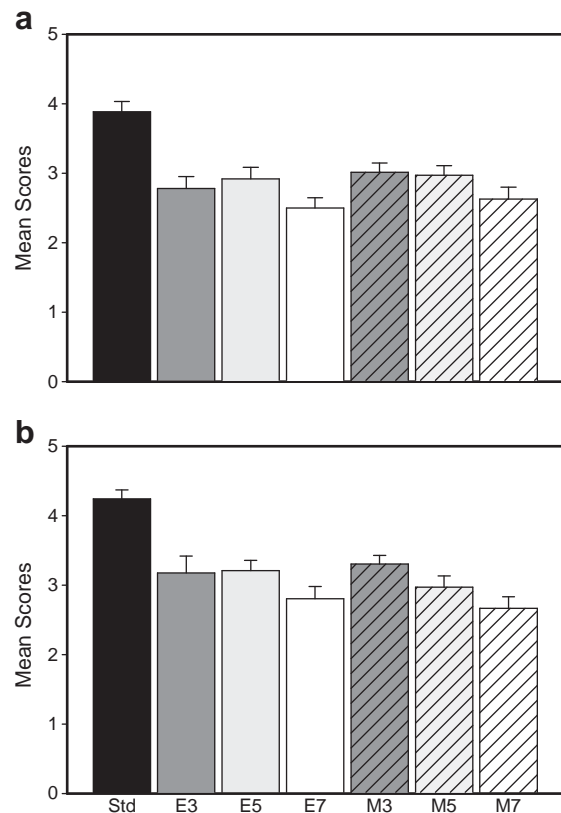


Fig. 6 – Mean scores of a) pleasantness and b) fittingness behavioral ratings in the y axis. Each experimental condition and position is shown in the x axis. (Std indicates standard condition).

distinct cortical sources. The cognitive processes eliciting these brain responses are hence most likely different as well (Koelsch et al., 2001; Koelsch et al., 2005; Koelsch et al., 2006; Leino et al., 2007). In particular, the extraction of rules dictating a hierarchical structure of musical events seem to require generators in the prefrontal cortex, whereas for the extraction of sequential music rules determining the frequency ratio between two consecutive sounds, the auditory cortex plays a primary role.

4. Experimental procedures

4.1. Participants

Twenty-four right-handed participants (10 male, 14 female; age range, 18–30 years; mean age, 24.6 years) participated in the experiment. Of those 24, only 5 were new participants from whom we recorded new EEG data sets, whereas 19 were from the study of Leino et al. (2007). The original data set was complemented with the ERP data of the new subjects. In addition to redoing the ERP and statistical analysis, we performed source analysis to corroborate the difference between ERPs. Behavioral ratings of the musical sequences were further analyzed (not reported in Leino et al., 2007). Nine participants were rejected from the EEG analysis due to problems with the data acquisition (i.e., excessive noise in channels, technical problems, time constraints); hence, they were only included in the behavioral part of the study to

increase its statistical power (typically lower for behavioral tests as compared with electrophysiological tests). In total, data from 15 participants (5 male, 10 female; age range, 18–26; mean age, 24.3 years) were included in the ERP analysis and data from the 24 in the behavioral analysis. This study is an extension of the study of Leino et al. (2007), with an increased sample size, behavioral ratings, and source analyses. All participants had normal hearing and no musical expertise or explicit knowledge of music theory. They also reported having no audiologic, cognitive, neurologic, or linguistic (word finding, writing, reading, and speech production and comprehension) deficits. Written informed consent was received from all participants. Participants received compensation for taking part in the experiment. Ethical permission was obtained from the ethical committee of the Faculty of Behavioral Sciences, University of Helsinki.

4.2. Stimuli

The stimuli used in the experiment were digitally generated piano and organ chords organized into cadences. The stimulus chords were prepared according to the rules of voice leading of Western functional harmony and further edited to have equal duration and intensity. Each stimulus cadence consisted of seven 600 ms long chords. The last 50 ms of each chord was gradually faded out, and each chord in the cadence was separated from the next chord by a 5 ms silent period. Cadences consisting of chords played with a piano timber were created for 7 different experimental conditions and in 12 different keys. In the standard condition (control), each of the 7 chords in the cadence belonged to the same key and together they composed a simple chord sequence following the rules of the Western functional harmony. In the three Neapolitan conditions (ERAN3, ERAN5, ERAN7), one in the chords of the standard cadence was replaced with a Neapolitan subdominant (Sn). The Sn replaced the tonic chord of the cadence (position 3), the subdominant chord of the cadence (position 5), or the ending tonic chord of the cadence (position 7). In the three mistuned conditions (MMN3, MMN5, MMN7), one of the chords of the standard cadence was replaced by a mistuned major triad (Mn), in which the fifth of the chord (at pitch distance of a fifth, or seven semitones, from the lowest note of the chord; see Fig. 1) was increased by 50 cents. Mirroring the Neapolitan conditions, the mistuned chord replaced either the third tonic chord of the cadence (position 3), the fifth subdominant chord of the cadence (position 5), or the seventh tonic chord of the cadence (position 7).

During the EEG recordings, tonic chords played with an organ timber were used as target stimuli for the primary task performed by the participants. The deviant organ chords were uniformly distributed among conditions and matched with the piano chords in all aspects except for timber. The organ chord was presented twelve times in each condition, each time in a different key (approximately 8% of all cadences), and always replaced a tonic chord of the cadence.

4.3. Procedure

Each experimental condition was presented in 12 different keys, 144 times in total. Each cadence was presented 5 ms after the preceding cadence, preserving the musical meter in order to give an impression of real flowing music. The cadences in different

keys and with different experimental manipulations were presented in a random order, while participants were wearing headphones and sitting in a comfortable chair inside a sound-proof room. The stimuli were presented using the software Presentation 9.30 (Neurobehavioral Systems, Ltd.) at a volume of 50 dB above the individual hearing threshold of each participant, determined at the beginning of the experiment. A semi-attended experimental paradigm was used, in which participants were instructed to attend to the musical sequences and press the response button after hearing the chord played by an organ. The purpose of the task was to ensure that the participants were attending to the stimuli without asking him or her to attend to the Neapolitan or mistuned chords (Koelsch et al., 2002a). The stimuli were presented in 8 separate stimulus blocks of approximately 10 min each in duration, and the entire experiment was approximately 3 h including preparation.

The EEG was measured using the BioSemi measuring system (BioSemi, Inc., Netherlands; <http://www.biosemi.com>). The scalp EEG was recorded with 128 active scalp electrodes fitted into a stretching cap and following the BioSemi ABC position system. In addition, three active electrodes were placed on the participant's nose and mastoid areas, respectively, and four more electrodes were placed around the eyes to monitor eye muscle activity. Twenty-four bit EEG data were recorded with BioSemi ActiView 5.32 using no reference (standard BioSemi acquisition method), with a sampling rate of 2048 Hz and a recording bandwidth of up to 417 Hz.

After the EEG measurements, the participants were instructed to listen to 28 cadences in different keys taken randomly from each of the 7 experimental conditions. Each experimental condition was repeated 4 times in different random keys. Participants rated each cadence according to valence and fittingness on 5-point scales (with 1 being the lowest score and 5 the highest) by answering to the following questions: "how pleasant did you find the melody?" and "how well did you think the chords of the melody fitted together?"

4.4. ERP analysis

Pre-processing and data analysis were performed with Brain Electric Source Analysis (BESA version 5.2; Berg and Scherg, 1994; Miltner et al., 1994). The EEG data for each participant were re-sampled offline for ERP analysis to a sampling rate of 256 Hz. We averaged the ERPs for each condition and cadence. The epoch was 600 ms starting from target-chord onset (the third, fifth, or seventh chord of the cadence). As a pre-stimulus baseline, we used a 100 ms period preceding the onset of the target chord. Channels with excessively noisy data (skin potentials and high frequency noise) were rejected, and artifact rejection was performed in BESA. Before averaging, the EEG data were filtered with a 0.5 Hz high-pass filter. After averaging, the ERP data were filtered with a low-pass filter of 40 Hz and re-referenced to the average of the mastoids. Difference waveforms were calculated by subtracting the responses to the standard chords from those to the Neapolitan or mistuned chords. The ERP data were then statistically evaluated using repeated-measures analyses of variance (ANOVA) with the mean ERP amplitude as the dependent variable.

First, the mean ERP amplitudes were calculated for each participant and condition from a 40 ms time windows

surrounding the grand-averaged peak at the Fz electrode (channel 21 in the BioSemi system). Then the mean amplitude data were analyzed using repeated-measures ANOVA with ERP component (levels: ERAN, MMN) and position (levels: 3, 5, 7) as within-subject factors. Second, the mean amplitude values were computed for four regions of interest (ROIs): left anterior (C25, C26, C32, D3, D4), right anterior (C3, C4, C10, C12, C13), left posterior (A5, A6, A7, A8, A18), and right posterior (A31, A32, B3, B4, B5). The data were then analyzed again using a four-way repeated-measures ANOVA with ERP component (ERAN–MMN), position (3, 5, 7), distribution (anterior–posterior), and hemisphere (right–left) as within-subject factors. For all statistical analyses, type I errors were controlled for by using Mauchly's test and the Greenhouse–Geisser epsilon when appropriate. The alpha-level for all statistical analysis was .05, unless stated otherwise. After statistical evaluation, the grand-average ERP waveforms were filtered with a 10 Hz low-pass filter for illustration purposes only.

4.5. Source analysis

Discrete source localization was performed with the Brain Electrical Source Analysis (BESA version 5.2) software (Berg and Scherg, 1994). The 4-shell spherical head model was used. In a first exploratory analysis aimed at determining the number and the starting locations of the source models, we performed the principal component analysis (PCA) for each participant and condition. We then studied the distribution of the resulting PCs and considered their physiological feasibility. The number and locations of the acceptable sources were fed into the subsequent analysis step. A regional source analysis was performed for the time window of 40 ms around the individual peaks of the global field power (GFP) curves for each experimental condition (ERAN3, ERAN5, ERAN7, MMN3, MMN5, MMN7). Regional sources (RS) are more stable than dipoles in the presence of noise because they model the dipolar current flow in the three Cartesian directions. The source analysis was performed in each participant with a residual variance (RV) < 20%. The first two RS fitted were symmetrically constrained because, in the individual data, stability is low and the noise is high; hence, this procedure was applied in order to avoid noise from moving the encephalic regional sources to the middle and outside of the brain. Also, this was done because of the physiological assumption that the sources of the ERAN and MMN are typically located in similar structures of the two cerebral hemispheres (e.g., Brattico et al., 2008; Maess et al., 2001). Next, we fitted more RS taking the PCA with an explanatory variance percentage above 1% as a reference for the number of possible sources. The first two symmetric RS fitted in each participant explained > 80% of the observed signal in all cases, with corresponding activity shown in the waveforms. Therefore, those two RS were considered as the main sources of MMN and ERAN activity respectively, and used for further analysis and plotting.

The coordinates of the resulting RS were registered according to the Talairach coordinate system (Talairach and Tournoux, 1988) for each condition (ERAN3, ERAN5, ERAN7, MMN3, MMN5, MMN7) and participant ($N=15$). In this coordinate system, the x -axis of the brain passes through the two pre-auricular points with positive to the right, the y -axis passes through the nasion and is perpendicular to the x -axis (positive to the front), and the z -axis points up and is perpendicular to the xy -plane (positive

upwards). The differences in the coordinate locations between the ERAN and MMN regional sources were separately studied for each axis (hemispheres were not taken into account because the RS were symmetric) with repeated-measures ANOVA with ERP component (levels: ERAN, MMN) and position (levels: 3, 5, 7) as within-subject factors. Finally, the mean coordinates of the RS were computed for the x , y , and z axes in all conditions and plotted. To show the localization of the individual and mean RS localization, we superimposed them on MRI images using BrainVoyager Brain Tutor software (<http://www.brainvoyager.com/BrainTutor.html>). This software also provides localization of cortical regions according to the Brodmann areas (BA).

Considering the uncertainty related to a single source analysis solution due to the inverse problem, we decided to perform an additional source analysis with Statistical Parametric Mapping (SPM 8; <http://www.fil.ion.ucl.ac.uk/spm>; Kiebel and Friston, 2004a; Kiebel and Friston, 2004b). SPM 8 uses Multiple Sparse Priors (MSP), an L2-norm-like approach to the inverse problem in which hundreds of patches of cortex are treated as spatial priors within a parametric empirical Bayesian framework (Friston et al., 2008). The Bayesian approach is a statistical method used to incorporate a priori information into the estimation of the sources and can result in linear or non-linear estimators. The types of a priori information include information on the neural current, the sparse focal nature of the sources, combined spatial and temporal constraints as well as strategies to penalize ghost sources, among others (multiple constraints) (Friston, 2007). After this, it performs a group inversion where subjects are pooled over to optimize the MSP before inverting any single subject (Litvak and Friston, 2008). It uses canonical cortical mesh (inverse-normalized), obviating the need for complex manual creation of individual cortical meshes from MRI, providing a mapping with a template in MNI space and allowing statistics across subjects. Then, it creates statistic parametric maps to test for topographical differences in ERP amplitude across the scalp and time. Overall, it provides several constraints to minimize human manipulation. The data from each subject are transformed into two-dimensional sensor-space (interpolated from 128 channels) and time window as a third dimension. This transformation produces three-dimensional spatiotemporal maps of the ERP. These maps can be then compared to localize condition effects using standard mass univariate statistical parametric maps in the fMRI way, by relying on t or F statistics to test for effects that are localized in peristimulus time.

For this analysis, the ERP data were first converted to SPM format, and subsequently, we assigned sensor positions and performed co-registration using BEM (boundary element method) head model and group inversion. After the inversion, we created statistical maps (images) for the subsequent general linear model (GLM) analysis. We created baseline images within the window of -100 to 0 ms to contrast with the conditions. Subsequently, we individually created images for the ERAN and MMN conditions using average windows of 100 ms around the individual peak location (between latencies 100 and 300 ms). Then, we performed the group analysis with a paired t -test (condition > baseline) for each condition and an uncorrected p -value of 0.001. As the locations of the MMN main sources are suggested to be located in superior temporal gyrus (STG) and the ERAN sources are in inferior frontal gyrus (IFG), we performed small volume correction (SVC) for these locations using IFG and STG maps,

respectively, included in the MarsBaR Toolbox (Brett et al., 2002) as bounding masks and a constraint of 4 mm for minimum spatial separation between peaks. For illustration purposes, we used the MRI template included in SPM 8 (single subject T1).

4.6. Behavioral analysis

We conducted two different analyses of the behavioral ratings, one for the ratings of pleasantness and another for ratings of fittingness of chords. Participants rated each cadence according to valence and fittingness on 5-point scales (with 1 being the lowest score and 5 the highest) by answering the following questions: “how pleasant did you find the melody?” and “how well did you think the chords of the melody fitted together?”

The variables were then compared using the non-parametric Friedman’s ANOVA with the Exact test method. We compared harmonically incongruous chords (ERAN3, ERAN5, ERAN7) vs. mistuned chords (MMN3, MMN5, MMN7) and the three positions within the cadence (3, 5, 7). Post hoc tests were performed using non-parametric Wilcoxon tests with Bonferroni correction (significance level = .0167), contrasting positions of harmonically incongruous chords (ERAN3-ERAN5, ERAN5-ERAN7, ERAN3-ERAN7), and positions of pairs of mistuned chords (MMN3-MMN5, MMN5-MMN7, MMN3-MMN7). We then plotted the data using mean scores as the y value in a bar graph (T = smaller sum of ranks, r = effect size).

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