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Responses to deviants are modulated by sub-threshold variability of the standard

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Abstract

Auditory mechanisms automatically detect both basic features of sounds and the rules governing their presentation. In the oddball paradigm, the auditory system detects the "sameness" (or no-variability) rule when the same reference tone is consistently repeated. We now used two oddball protocols, the classical one with a fixed reference, and a modified one with a jittered reference to determine whether the auditory system can detect sub-threshold violations of "sameness". We found that the response to the repeated standard was not modified by the small jitter. However, the response to the frequency oddball was smaller under the jittered protocol, indicating hypersensitivity to "sameness". The sensitivity to jitter was largest when the oddball deviated by 8%, smaller for 40% and disappeared at 100% deviation, indicating that sensitivity to "sameness" is context dependent; namely, it is scaled with respect to the overall range of stimuli.

Introduction

When we are exposed to a sequence of repeated sounds, even while attending to other stimuli, we automatically produce implicit expectations that subsequent stimuli will have similar features. The mechanisms underlying these automatic processes have been extensively studied using ERP in an oddball paradigm. In the typical oddball paradigm, a sequence of homogenous sounds is presented with an occasional deviant stimulus. The unexpected deviation (oddball) produces an increased ERP response compared with that produced by the repeated standard. This difference wave is named mismatch negativity (MMN) (Naatanen, 1992; Naatanen, Paavilainen, Rinne, & Alho, 2007; Tiitinen, May, Reinikainen, & Naatanen, 1994). MMN peaks 150 – 250ms after the deviation from regularity and is produced mainly by the auditory cortex (with a frontal contribution: Alho, Woods, Algazi, Knight, & Naatanen, 1994; Deouell, Bentin, & Giard, 1998).

In frequency oddball, it has been shown that, within a very broad frequency range spanning 2 to 40% deviations, the response to the oddball increases with the increase in deviation from the standard frequency (Baldeweg, Richardson, Watkins, Foale, & Gruzelier, 1999; Naatanen, 1992; Novitski, Tervaniemi, Huotilainen, & Naatanen, 2004; Pakarinen, Takegata, Rinne, Huotilainen, & Naatanen, 2007; Tiitinen, May, Reinikainen, & Naatanen, 1994). This response has been interpreted as composed of two components. The first, which increases with increasing frequency deviation, was attributed to the activation of less-adapted frequency tuned neurons (Naatanen, Paavilainen, Rinne, & Alho, 2007). The second

component was attributed to the detection of regularity violation, in this case, the violation of "sameness", established by the repeated fixed-frequency reference tone. This violation is thought to be detected by a specialized regularity-tracking neuronal population (Hari, Rif, Tiihonen, & Sams, 1992; Naatanen, Jacobsen, & Winkler, 2005; Naatanen, Paavilainen, Rinne, & Alho, 2007; Picton, Alain, Otten, Ritter, & Achim, 2000). In the context of a fixed-reference tone, there is evidence that a deviant tone produces an additional, delayed response component which is not found when this tone is not a deviant and hence does not violate the regularity of simple repetition (Jacobsen, Horenkamp, & Schroger, 2003; Jacobsen & Schroger, 2001; Jacobsen & Schroger, 2003; Jacobsen, Schroger, Horenkamp, & Winkler, 2003; Schroger & Wolff, 1996).

More complex regularities, that cannot be explained by simple adaptation within a single dimension, have also been reported (Bendixen, Prinz, Horvath, Trujillo-Barreto, & Schroger, 2008; Naatanen, Paavilainen, Rinne, & Alho, 2007; Paavilainen, Arajärvi, & Tager-Flusberg, 2007; Picton, Alain, Otten, Ritter, & Achim, 2000), thus substantiating the suggestion of an automatic mechanism for abstract rule detection (often termed "genuine MMN"). It had been suggested that these regularities are detected by higher-level neuronal populations (Bendixen, Prinz, Horvath, Trujillo-Barreto, & Schroger, 2008; Kujala, Tervaniemi, & Schroger, 2007; Naatanen, Jacobsen, & Winkler, 2005; Naatanen, Paavilainen, Rinne, & Alho, 2007; Winkler & Czigler, 1998; Winkler et al., 2003). It was further posited that in contrast to simple adaptation where the magnitude of the response increases with deviation when rule violation is detected, the response operates as "all-or-none". In other words, the magnitude of the response to rule violation does not depend on the magnitude of violation. The concept of a categorical (i.e. binary; all-or-none) response to the detection of rule violation was assessed for the case of a frequency oddball by Horvath et al., 2008. They concluded that the response to rule violation (the "genuine MMN") was indeed categorical.

The concept of categorical rule detection is intriguing as it contrasts with an alternative, analog evaluation of the degree of surprise. It implies that the system is insensitive to the degree of regularity violation. The case of "sameness" is important to study as regards this distinction since: 1) the most commonly studied oddball paradigm is based on this simple regularity; 2) the resolution of the mechanisms underlying rule detection can easily be tested by examining whether a very small, near-threshold violation of "sameness" is detected as rule violation (e.g. Jacobsen & Schroger, 2001; Schroger & Wolff, 1996); 3) the "all-or-none" phenomenon can be investigated, for example, by assessing whether rule detection is sensitive to the global context. A simple change of context can be achieved by modifying the degree of oddball deviation. The categorical interpretation predicts that the magnitude of the response to rule violation will be invariant to the degree of oddball deviation.

To test the system's resolution for detecting small deviations from "sameness" we used two protocols: the typical oddball protocol with a fixed-standard tone and a jittered-standard protocol (inspired by Schroger & Wolff, 1996) with the same average frequency. The magnitude of the jitter (9 different frequencies, spanning a range of $\pm 2\%$ in steps of 0.5% around the average) was chosen to be just under the threshold level of detection, as suggested by earlier MMN studies (i.e. a 0.5% deviation does not produce any measurable MMN response: Berti, Roeber, & Schroger, 2004; Novitski, Tervaniemi, Huotilainen, & Naatanen, 2004; Pakarinen, Takegata, Rinne, Huotilainen, & Naatanen, 2007; Tiitinen, May, Reinikainen, & Naatanen, 1994). To assess context effects on the degree of sensitivity to "sameness violation" we administered three degrees of frequency deviation: 8, 40 and 100%. The choice of this broad range was based on single unit studies, which typically report relatively crude frequency tuning curves in the auditory cortex (Ehret & Schreiner, 1997; Howard et al., 1996; Kajikawa, de La Mothe, Blumell, & Hackett, 2005; Moore, 1997;

Recanzone, Guard, & Phan, 2000; though see Bitterman, Mukamel, Malach, Fried, & Nelken, 2008). Based on these studies we assumed that this small jitter would not be detected by adaptation mechanisms since frequency tuning is quite broad, and therefore the responses to the fixed-reference and the jittered-reference should not differ.

If indeed the two protocols induce the same adaptation mechanisms, and hence the same response to the fixed and jittered standards, any difference in the response to the deviant under these two conditions can be attributed to the violation of the "sameness" rule ("genuine MMN"). Moreover, it would indicate that violations from "sameness" are detected with hypersensitivity; i.e., with greater sensitivity than that revealed by simple adaptation mechanisms. The hypersensitivity prediction is supported by many previous studies reporting MMN responses even to very small (~2%) deviants (Baldeweg, Richardson, Watkins, Foale, & Gruzelier, 1999; Novitski, Tervaniemi, Huottilainen, & Naatanen, 2004; Pakarinen, Takegata, Rinne, Huottilainen, & Naatanen, 2007; Tiitinen, May, Reinikainen, & Naatanen, 1994; Berti, Roeber, & Schroger, 2004; Horvath et al., 2008). Finding hypersensitivity in this protocol would indicate that MMN responses to very small deviations reflect the rule-violation mechanism.

The second question we addressed was the impact of stimulation context. The different contexts induced by different degrees of oddball deviations are expected to activate the same adaptation mechanisms for each of the protocols. Hence, the jitter effect (Fixed MMN-Jittered MMN) under all degrees of deviation is expected to directly measure rule violation. If its magnitude changes as a function of oddball deviation this would indicate that violation detection mechanisms are gradual rather than categorical.

Method

Subjects

Twenty-two subjects (7 males, 3 left-handed; 26 ± 5.5 years of age) participated in the study and 19 completed the whole set of measurements. Four subjects had previous experience with auditory frequency discrimination tasks. All subjects reported normal hearing and no known neurological disabilities. All subjects signed a consent form to participate in the study.

Experimental Procedure

Electrophysiological recordings were performed while the auditory passive oddball protocols were administered. Subjects were seated in a sound-attenuated chamber. During the recording session they were presented with sequences of tones while watching a silent movie. The movie screen was narrowed and centered to reduce eye movements. The subjects were asked to sit comfortably so that movements during the recordings would be minimal. The experimenter's instructions were to concentrate on the movie and to pay no specific attention to the sounds.

Each recording session consisted of 2 consecutive measurements (see below), separated by a 2–5 minute break during which the subjects were encouraged to rest and eat/drink while seated in the chamber.

Stimuli

The oddball paradigm was used to construct two types of protocols:

1. Fixed Standard protocol – the typical oddball protocol. Stimuli were sequences of 50ms (including 5-ms rise and fall times) pure tones with a 1000Hz standard tone ($p=0.90$) and a deviant tone ($p=0.1$). Three deviance conditions were used in

separate sessions, respectively: 1080Hz (8% deviance), 1400Hz (40% deviance) and 2000Hz (100% deviance; the latter deviance condition may be slightly different because it is the first harmonic of the standard tone and therefore may be subject to additional harmonic related processes. However, harmonic processes are thought to be mainly induced by richer, chord stimuli, e.g. Doeller et al., 2003 and Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002, rather than by pure tones, as used in the current study).

Each of the fixed standard conditions consisted of 1500 tones (i.e. 150 deviants). The tones were presented in a pseudorandom manner, so that each deviant tone was preceded by at least three consecutive standards.

2. **Jittered Standard** protocol – under this protocol 10 types of stimuli were used; nine ($p=0.1$ for each) were clustered around 1000Hz (hence the name "jittered standard"): 980, 985, 990, 995, 1000, 1005, 1010, 1015, 1020 Hz. The tenth was the deviant: 1080, 1400 or 2000Hz. The different deviance conditions were administered in separate sessions.

Under the jittered standard protocol each of the deviance conditions consisted of 2500 tones. The tones were presented in a pseudorandom manner, so that each deviant tone was preceded by at least 5 jittered standards. Stimuli were 50ms long (including 5-ms rise and fall times) and were binaurally delivered via headphones. The stimulus onset asynchrony (SOA) was evenly chosen from a range of 480–580 ms.

Sequence of recording sessions

Each recording session included consecutive measurements of the fixed and jittered standard protocols, both with the same specific oddball. Each subject participated in two sessions with the same oddball, hence counterbalancing the order of the fixed and jittered standard. Thus, subjects participated in 6 sessions ($3 \text{ deviants} \times 2 \text{ sequences of jittered and fixed standard protocols}$). To partially control for the potential interactions between session order and overall sensitivity to degree of deviance, we used two sequences of sessions: 40%; 100%; 8%; and a reversed order: 8%; 100%; 40%. Half of the subjects began their recordings with the first order and the other half with the reversed order.

The interval between the sessions varied from several days to several weeks.

EEG Recording and Averaging

EEG was recorded from 32 active Ag-AgCl electrodes mounted on an elastic cap using BioSemi ActiveTwo tools. The electrode sites were based on the 10–20 system (American Electroencephalographic Society, 1991). Two additional electrodes were placed over the left and right mastoids. Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from electrodes on the infraorbital and supraorbital regions of the right eye in line with the pupil.

EEG and EOG signals were sampled at 256 Hz, amplified and filtered with an analog band-pass filter of 0.16 – 100Hz. Off-line analysis was performed using BrainVision Analyzer software. EEG was referenced to the averaged mastoids, and was digitally filtered using a band-pass of 1–30 Hz. Artifact rejection was applied to the non-segmented data according to the following criteria: any data point with an EOG or EEG $> \pm 100 \mu\text{V}$ was rejected along with the data points in a span of $\pm 300\text{ms}$ around it. In addition, if the difference between the maximum and the minimum amplitudes of two data points within an interval of 50 ms exceeded $100 \mu\text{V}$, the data point along with the data points in $\pm 200 \text{ ms}$ around it were rejected. Trials containing rejected data points were omitted from further analysis, as well as the first three trials of each block. For ERP averaging, the EEG was parsed to 500 ms epochs

starting 100 ms before the stimulus, and then averaged separately for each condition and for each stimulus type. The averaged responses were then again filtered in order to stabilize the amplitude and latency quantification of the MMN. Frequencies higher than 12 Hz were filtered out. The baseline was adjusted by subtracting the mean amplitude of the (100ms) pre-stimulus period from all the data points in the averaged epoch.

In all recording sessions, all subjects remained with several hundred fixed standard segments, several hundred jittered standard segments (average response to the 9 jittered-standard frequencies) and more than 80 deviant segments (except one subject who once remained with only 60 clean deviant segments).

The sensitivity of the auditory cortex to deviant events was measured as follows: for the fixed standard protocol, ERPs elicited by standard tones were subtracted from those elicited by deviant tones. For the jittered standard protocol, ERPs elicited by deviant tones were subtracted from the average response to the nine standards.

To verify the expected polarity diversion of the MMN waves at the mastoid electrodes and to study the scalp distribution of the MMN waves to compare to the data reported in Baldeweg and colleagues (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002) the recordings were re-referenced off-line to the nose electrode. The re-referenced recordings were then processed according to the abovementioned description.

ERP Analysis

Raw responses—The responses of the counterbalanced fixed and jittered protocols were averaged for each deviance condition and separately for each subject.

MMN potentials

Calculation: MMN calculations were performed on the mastoids-referenced data. MMN peaks were defined as the most negative peaks between 100ms and 250ms post stimulus (Pakarinen, Takegata, Rinne, Huotilainen, & Naatanen, 2007). The amplitude and latency of the MMN peaks were manually obtained in a subject by subject manner for each condition separately. The grand average (across subjects) MMN waves and standard errors were also calculated.

Statistical Analyses: There were two manipulations in this study: 1) manipulation of the consistency of the standard (fixed vs. jittered); 2) manipulation of the degree of deviance (8, 40 and 100%). Therefore, 2×3 comparisons of MMN peak amplitudes were performed using analysis of variance (ANOVA) for repeated-measures corrected for sphericity violations. The within-subject factors were Protocol (Fixed versus Jittered) and Deviance condition (8%, 40% and 100%). Main effects of deviance condition and protocol as well as simple contrasts for the deviance condition variable (3 levels) were obtained.

Since the number of stimuli in the fixed and jittered conditions was not equal, we also performed all the above analyses with an equated number of stimuli. We equated the number of stimuli by cutting out the last part (1000 stimuli) of the data from the Jittered condition when presented after the Fixed condition, and the first part when presented before the Fixed condition. The significance of the effects reported below remained.

To study test-retest replicability of MMN under the experimental conditions we 1) measured peak amplitudes and calculated Pearson's test-retest correlations; 2) conducted a City-Block Distance analysis (Edgington, 1980; Schroger, 1998). City-Block Distance (a special case of "Minkowski-distances") can be used as a measure of the similarity of the distributions/

means of two sets of repeated measures without any prior assumptions regarding the distribution of the data points.

Results

The responses to the standard tone were very consistent across conditions. As shown in Figure 1A, they did not differ between the jittered and fixed standard protocols, in line with the prediction based on adaptation in neurons with broad frequency tuning (Ehret & Schreiner, 1997; Howard et al., 1996; Kajikawa, de La Mothe, Blumell, & Hackett, 2005; Moore, 1997; Recanzone, Guard, & Phan, 2000). To verify this observation, we calculated the response to each of the near-standard frequencies in the jittered protocol and compared them to the average response in the fixed protocol. Figure 1D shows the grand average responses to 1000Hz in the fixed versus responses to 1000Hz and to 980Hz in the jittered protocol, in the 40% deviance condition. The responses to the fixed and jittered 1000Hz overlap, indicating that the standard response was equally adapted. Moreover, the response to the most distant 980Hz standard overlaps with the response to the fixed and jittered 1000Hz, indicating similar adaptation states among the 9 standard frequencies we used. This result demonstrates that the jitter was indeed sub-threshold for adaptation mechanisms operating on the standard tone. It should be noted that subjects could differentiate between the fixed and the jittered-standard protocols, though this difference was not salient, according to their reports.

The responses to the deviants increased with increasing degree of deviance, as shown in Figure 1B. Peak responses to deviants were not saturated within the tested range and increased both between 8 and 40% and between 40 and 100% deviance, indicating that neurons whose best frequency is around 1400Hz are still partially adapted by the standard frequency. Thus, the broad tuning of the deviance effect suggests that this effect is also mediated by neurons with broad frequency tuning. Additional assessments that we administered to 4 subjects using 300% deviance (4000Hz, not shown) showed no further increase in response, suggesting that neurons whose best frequency is around 2000Hz are not adapted by 1000Hz.

A repeated measures ANOVA on MMN peak amplitudes with deviance condition (8, 40, 100%) and protocol (fixed vs. jittered) as within-subject factors showed a significant deviance effect (Deviance effect; $F_{(2,36)}=83.4$, $p<0.0001$, corrected for sphericity violations, Greenhouse-Geisser Epsilon = 0.85), a significant jitter effect (Fixed MMN > Jittered MMN; $F_{(1,18)}=7.4$, $p<0.014$) and a significant interaction between the two main effects ($F_{(2,36)}=11.4$, $p<0.001$, corrected for sphericity violations, Greenhouse-Geisser Epsilon = 0.77).

Thus, although the small jitter ($\leq 2\%$) had no effect on the response to the standard, it had a significant effect on the response to the deviant. Jittering the standard significantly reduced the responses to 8 ($p<0.0001$ in a paired, two-tailed t-test) and to 40% ($p<0.001$) deviants (dashed versus solid lines in Figure 1B). On the other hand, responses to 100% deviant were not affected by the jitter (the minor opposite difference, shown in Figure 1B, was not significant ($p=0.5$ in a paired, two-tailed t-test)).

Since the responses to the standard did not change, the MMN responses (i.e. deviant minus standard; Figure 1C) reflect the effects on the deviant.

Figure 2 demonstrates the jitter effects; i.e., the difference waves obtained by subtracting the jittered ERPs from the fixed ERPs for the corresponding standards (fixed 1000Hz – average across 9 standard frequencies) - top, deviants (fixed deviant – jittered deviant) - middle and MMN (fixed MMN – jittered MMN) – bottom, separately for each deviance condition. The

jitter effects were first calculated for each subject separately and the plots denote the grand average of these effects. It can clearly be seen that there is no jitter effect in the responses to the standard. The difference waves (Figure 2A) are not different from zero at any point in time. On the other hand, the responses to 8 and 40% deviants were significantly reduced under the jittered protocol (Figure 2B). The significant interaction between the deviance effect and the jitter effect found for the MMN peak amplitudes can be seen in Figure 2C. This interaction is also evident in the responses to the deviants. Specifically, the difference between the fixed and jittered deviant (Figure 2B) is maximal under 8%, intermediate under 40%, and disappears under 100% deviance.

To assess whether the scalp distributions under the jittered and fixed protocols were similar, we plotted a sample of the recordings made in several electrodes. The recording electrodes plotted in Figure 3 were chosen on the basis of previous findings that the MMN recorded at the mastoids may be differentially affected by stimulus repetition than that recorded by frontal electrodes (Baldeweg, Williams, & Gruzelier, 1999). Furthermore, it was suggested that the mastoids reflect mainly the temporal generator/s whereas frontal electrodes are more affected by other sources (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002). Figure 3 shows that for the 8 and 40% deviance conditions, which show a significant jitter effect, the distribution of the jittered and fixed MMN is similar. Thus, at least within the resolution of our assessments, we found no evidence for spatially segregated sources contributing differentially to the MMN under these conditions.

Since subjects performed each deviance condition twice, once with the jittered protocol first and once with the fixed protocol first (the order of these two session types was counterbalanced across subjects) we could assess test-retest reliability of the MMN response under each deviance condition (Figure 4). The test-retest correlation of the 8% deviance conditions were not significant, as shown in Figure 4 left plots, either for the fixed or for the jittered protocols. This result may, at least partly, stem from the difficulty in evaluating the exact peak for some subjects whose MMN responses at 8% were quite small, with a low signal-to-noise ratio. Variability in the period separating the test and the retest measurements may have also reduced the test-retest correlations (Pekkonen, Rinne, & Naatanen, 1995).

However, test and retest measures were significantly correlated for the MMNs recorded with larger deviants, both under the fixed and under the jittered protocols, as shown in the middle and right plots of Figure 4, in line with previous reports (Kathman, Frodl-Bauch, & Hegerl, 1999; Tervaniemi et al., 1999; Tervaniemi et al., 2005). The difference in test-retest correlations between the smaller and larger deviants is consistent with previous findings that larger MMNs produce better test-retest correlations because of a better signal-to-noise ratio (Kathman, Frodl-Bauch, & Hegerl, 1999). Interestingly, the highest test-retest correlation was found for the 100% deviance MMN recorded under the jittered standard protocol ($R^2=0.65$, $p<0.001$).

Average MMNs did not change across assessments and the linear regression lines (slope <1 and intercept with the diagonal) showed the expected tendency of regression-to-the-mean.

To corroborate our parametric test-retest analysis, we also conducted a non-parametric post-hoc analysis of the City-Block Distance (Edgington, 1980; Schroger, 1998), which yielded similar results. For the 8% deviance, the measured test-retest distance was smaller than a non-significant fraction of the observed measures after permuting the datasets (74% and 83% for the fixed and jittered protocols, respectively). On the other hand, for both 40 and 100% deviance, the measured distances were smaller than more than 96% of the distances obtained after permutation. Taken together, these analyses show that at least for large

deviants, although inter-subject variability was substantial, the within subject test-retest is quite reliable.

To test the consistency of the jitter effect across subjects, we examined the relations between the MMN magnitudes of single subjects under the fixed and jittered protocols, as shown in Figure 5. Dots under the diagonal indicate a jitter effect; i.e. a smaller MMN under the jittered than under the fixed standard protocol. In the 8% deviance almost all dots are under the diagonal, indicating that all subjects showed a jitter effect. For the 40% deviance the vast majority of the dots are under the diagonal, whereas for the 100% deviance there are more dots above the diagonal, though the linear regression line almost overlaps the diagonal. Figure 5 further illustrates that linear regression reliably characterizes the relations between the jittered and fixed MMNs across the population. This reliability peaks for 40% deviance where linear regression captures nearly 90% of the cross-subject variability in the responses (Figure 5, middle plot; $R^2=0.87$, $p<<0.001$). This high correlation suggests that although both the overall MMN response and the jitter effect differed greatly between individuals, the jitter effect could be reliably assessed using a within-subject assessment, by testing whether a participant's data point was near the expected fixed-jitter relation. A third characteristic is the slope of the linear regression. It is smaller than 1, indicating that the jitter effect was larger for individuals with an overall higher MMN response. Note that the test-retest measurements were obtained days to several weeks apart, whereas the Fixed and Jittered protocols of the same deviance condition were measured in succession on the same day, though the plots reflect the average of these two (test and retest) sessions for each condition.

Discussion

Using the oddball paradigm, we examined the sensitivity of the auditory system to a small jitter in the simplest case of regularity – sameness, in other words, an accurate repetition of the standard. The design of the jittered paradigm was inspired by the paradigm devised by Schroger & Wolff (1996). In their paradigm, they eliminated the repetition of the standard by designing a control protocol composed of several broadly spaced tones with equal probability (and thus contained no oddball). Our focus was somewhat different, in that we examined the resolution of sameness detection compared to that of adaptation mechanisms. We therefore used a small frequency difference (0.5%) between tones in our jittered condition. We manipulated the stimulation context by using three levels of deviants: small (8%), intermediately large (40%) and large (100%), assessed in different sessions. We found that the response to the standard tone was not affected by this small jitter or by the degrees of deviance. The response to the deviant increased with increased level of deviance, from 8 to 40% and even from 40 to 100% under both protocols. Taken together, these findings indicate that the tuning of simple adaptation mechanisms is broad, and that the small jitter we introduced in the jittered protocol is indeed "sub-threshold" for detection by these mechanisms.

However, the response to the deviants was smaller under the jittered protocol, reflecting hypersensitivity to violations of the "sameness" rule, and indicating a separate mechanism which detects simple regularities such as sameness (or no-variability), in line with previous studies reporting specialized mechanisms for regularity detection (e.g. Winkler, 2007; Winkler & Czigler, 1998; Winkler, Karmos, & Näätänen, 1996). In addition, we found that sensitivity to the magnitude of the deviance and sensitivity to rule violation shared similar delays and scalp distribution, reflecting a similar processing stage rather than sequential evaluation.

The third finding is that the magnitude of the response to regularity violation depended on the overall stimulation context. It was largest for the smallest deviance (8%), smaller but

significant for the intermediate deviance (40%) and disappeared when the deviant was extremely different with respect to the magnitude of the jitter (100% deviance). This interaction cannot be explained by a different level of adaptation since only the "context" was modified, whereas the standard tone/tones and response to these standards remained the same.

Thus, the response to violation of regularity was not an all-or-none or categorical response. Rather, it was graded, and seemed to be normalized with the overall range of stimuli. These results are in line with models of predictive coding (e.g. Garrido, Kliner, Stephan & Friston, 2009). According to the Garrido et al. model, the neural response represents a suppressed prediction error. Predictions formed at higher levels interact with bottom-up driven responses: the more salient the prediction, the stronger the suppression of the response to a stimulus that matches the prediction. When the prediction fails, the suppression becomes ineffective, leading to an error response. The error response (i.e. the response to the unexpected deviant) is expected to depend on both the magnitude of the violation and the strength of the prediction. In our case, when the standard was jittered, the predictive model lost its strength, leading to a reduction in the relative error response (Jittered MMN) compared to the Fixed MMN. The impact of the uncertainty induced by the jitter varied, since the proportion of the jitter with respect to the overall violation (stimulus range) changed. For the smallest deviant (8%) it was 0.25 of the overall violation, and therefore the MMN response was significantly affected. However, when the deviant was 100%, the jitter spanned only 1/50 of the violation and therefore did not affect the magnitude of the MMN. This graded characteristic seems ecologically beneficial since it automatically integrates the global context (stimulus range) and scales its predictions accordingly.

Characteristics of the deviance and jitter effects

Although the MMN signals were calculated by subtracting the response to the standard from the response to the deviant, the MMN in our study directly reflects the change in the responses to the deviants since the response to the standard remained the same. The sensitivity to the small jitter indicates that some aspect of the tuning is narrow. However, this aspect is not manifested in any reduction in the response to the standard when it is jittered by up to 2%. Moreover, the dynamics of the sensitivity to the deviance implies broad tuning, since the MMN magnitude is not saturated at 40% deviance and further increases when the deviance is 100%. These results demonstrate different degrees of frequency resolution within the same response, the response to the oddball.

In Figure 6 we re-plot the data illustrating these broad and narrow tuning curves, respectively. Figure 6A shows the MMN in the jittered protocol for 8% (left), 40% (middle) and 100% (right) deviants. We propose that the MMN produced in this protocol mainly (see some caveats below) reflects the sensitivity of adaptation mechanisms. The deviance effect can be attributed to the smaller degree of adaptation to deviant frequencies, which is reflected in the earlier N1 component, as suggested in the literature (Horvath et al., 2008; Jaaskelainen et al., 2004; May & Tiitinen, 2004; Jacobsen & Schroger, 2001; May & Tiitinen 2010).

Figure 6B illustrates the jitter effect; i.e., the difference between the responses to the deviant tone under the fixed and the jittered-standard protocols revealed in the responses to 8% (left), 40% (middle) and 100% (right) deviants. We propose, as claimed elsewhere, that it reflects the mechanism that tracks the violation from the "sameness" rule. The magnitude we found for the rule-violation response is relatively small. It is similar to that obtained in the Schroger & Wolf paradigm (1996), where violation from sameness was much larger. However, their paradigm was mainly designed as a "proof of existence" of a rule-violation mechanism, and adaptation mechanisms led to an underestimation of its magnitude. Other

studies of rule-violation MMN recorded larger magnitudes (Schroger, Bendixen, Trujillo-Baretto, & Roeber, 2007; Tervaniemi, Rytönen, Schroger, Ilmoniemi, & Naatanen, 2001).

Thus, reports regarding the magnitude of rule-violation vary, further supporting the notion of a graded response. These range from $\sim 2 \mu\text{V}$ (Schroger, Bendixen, Trujillo-Baretto, & Roeber, 2007; Tervaniemi, Rytönen, Schroger, Ilmoniemi, & Naatanen, 2001) to $\sim 0.5 \mu\text{V}$ (Bendixen, Prinz, Horvath, Trujillo-Barreto, & Schroger, 2008; Paavilainen, Arajärvi, & Tager-Flusberg, 2007; Tervaniemi, Saarinen, Paavilainen, Danilova, & Naatanen, 1994). This implies that the magnitude of the abstract MMN depends on measurement parameters such as salience (or accessibility) of the rule and the salience of its violation. Salience may stem from larger physical deviations or greater psychophysical sensitivity (e.g. through training). We used a very small manipulation and obtained a "clean" though small rule-violation effect. It would be of interest to assess whether increasing the variability (e.g. increasing the jitter) would induce a larger effect, suggesting that the MMN response under the jitter-standard protocol also contains a small "sameness" detection response.

Our findings that the magnitude of the rule-violation response is graded differ from conclusions in Horvath et al., (2008), who studied rule violation with different degrees of oddball deviations, and reported an all-or-none response. However, a careful look at their results shows that they also found that the magnitude of responses to rule-violation significantly depends on the degree of oddball deviation, though it was not significant across the entire range of deviants they measured. The decrease of significance is perhaps related to adaptation mechanisms masking some of the rule-violation response, specifically in the case of larger deviants.

Comparing the top and bottom panels of Figure 6 shows that the dynamics of the deviance response and the rule-violation response are similar. Specifically, they peak at similar latencies, as indicated by the vertical dashed lines. These mechanisms also have similar scalp distributions, as illustrated in Figure 3. Thus, they do not seem to originate from different sources that have different contributions to frontal vs. mastoid electrodes (see for example Baldeweg, Klugman, Gruzeller, & Hirsch, 2002).

Relation to neuronal and behavioral frequency selectivity

Tonotopic organization characterizes the auditory pathways from the periphery at least up to and including the primary auditory cortex (Yost, 2000). Though the width of cortical tuning curves is quite variable (Ehret & Schreiner, 1997; Kajikawa, de La Mothe, Blumell, & Hackett, 2005), the typical curves reported are broad (Recanzone, Guard, & Phan, 2000), in line with the broad tuning revealed by the MMN deviance effect. Intracranial recordings from human auditory cortex (Howard et al., 1996 and recently Bitterman, Mukamel, Malach, Fried, & Nelken, 2008), have also found frequency-specific responses. The overall shape of the physiological tuning curves corresponds to those found in behavioral studies (Moore, 1997).

However, recent findings show that frequency resolution largely depends on the assessment protocol. Behaviorally, Nahum et al. (Nahum, Daikhin, Lubin, Cohen, & Ahissar, 2010) found that frequency resolution depends to a great extent on the pattern of cross-trial stimulus repetition. Thus, with no cross trial consistency, frequency discrimination thresholds are $\sim 10\%$, but they decrease to $\sim 1\%$ when the frequency of the first tone is kept fixed across trials. Similarly, at the level of single neurons, Ulanovsky and colleagues (Ulanovsky, Las, & Nelken, 2003) reported that when measured with an oddball paradigm (high probability of standard frequency and low probability of oddball), A1 neurons became discriminatively sensitive to previously indiscriminable frequencies. The oddball paradigm used to measure the MMN is based on nearly maximal cross-trial stimulus regular repetition,

and therefore provides conditions that induce high resolution. In fact, MMN studies also often detect hyper-resolution, showing that even small deviants (~2%) induce a mismatch response (Berti, Roeber, & Schroger, 2004; Horvath et al., 2008; Menning, Roberts, & Pantev, 2000; Novitski, Tervaniemi, Huotilainen, & Naatanen, 2004; Pakarinen, Takegata, Rinne, Huotilainen, & Naatanen, 2007). This hyper-resolution was attributed to specific neuronal populations and mechanisms specialized for change detection, which differ from those underlying activity-induced adaptation (discussion in Naatanen, Jacobsen, & Winkler, 2005).

Our current data suggest that the protocol-specific extra sensitivity may indeed derive from additional mechanisms that detect inter-stimulus relations. The neural site and underlying mechanisms of such an evaluation cannot be determined from the current study. However, our finding that both jitter and deviant effects have similar temporal delays (~150–200ms) and a similar scalp distribution, together with the physiological findings of dynamics in tuning curve width, suggest that both mechanisms may be implemented in the same auditory cortex, perhaps by the same neuronal populations. This interpretation is in line with single unit results that suggest that both average and noise level may be automatically detected within the same processing stage and even within the same neurons (Petersen, Panzeri, & Maravall, 2009). Moreover, theoretical work has shown that both may affect the neuronal operating curve (Hong, Lundstrom, & Fairhall, 2008). The spatial overlap conclusion contrasts with an fMRI study (Opitz, Schroger, & Yes von Cramon, 2005), which reported a spatial segregation between these two sources. However, a subsequent MEG study (Maess, Jacobsen, Schroger, & Friederici, 2007) designed to re-examine the location of the brain sources of the "comparator-based" (rule-violation) MMN vs. "non-comparator-based" (adaptation related) effect did not replicate their result. Using the controlled paradigm applied in Schroger & Wolff (1996), they found spatially overlapping activities of non-comparator-based and comparator-based mechanisms of automatic frequency change detection in the auditory cortex.

Individual differences in the efficiency of simple adaptation and regularity detection mechanisms

Our findings suggest that to study the adaptation effect separately the jitter paradigm should be used, since it does not (or only to a small extent) induce the additional responses produced by mechanisms detecting maximal regularity. In fact, the test-retest response correlation in the jitter condition is highly reliable for large deviants (see Figure 4). On the other hand, to assess rule detection mechanisms, it is important to use a slightly variable standard as a comparison condition. The overall ERP and behavioral data suggest that frequency sensitivity reflects at least two separate mechanisms rather than a single one. Moreover, specific individuals may have a deficit in one and not in the other. For example, dyslexic individuals seem to have difficulties in increasing frequency resolution based on stimulus regularities (Ahissar, 2007; Ahissar, Lubin, Putter-Katz, & Banai, 2006), and may thus have a specific difficulty in the rule detection mechanism. This difficulty may impact the latency of the ERP components (Moisescu-Yiflach & Pratt, 2005) as well as their amplitudes. Notably, dyslexic subjects have no MMN when assessed with very small deviants (Baldeweg, Richardson, Watkins, Foale, & Gruzelier, 1999), which may mainly reflect the regularity detection mechanisms, whereas their MMN induced by very large deviants is unimpaired (Bishop, 2007; Schulte-Korne, Deimel, Bartling, & Remschmidt, 2001). Other populations with impaired MMN responses (Baldeweg, Klugman, Gruzelier, & Hirsch, 2002; Banai, Nicol, Zecker & Kraus, 2005; Dale et al., 2010; Kujala & Naatanen, 2001; Kujala, Tervaniemi, & Schroger, 2007; Kurylo, Pasternak, Silipo, Javitt, & Butler, 2007; Moberget et al., 2008) may also have differential deficits in these two mechanisms.

Our results suggest that parts of the protocol used in this study can be implemented in clinical evaluations, specifically to measure the efficiency of the rule-extraction mechanism, whose magnitude is well predicted by the magnitude of the jittered response. For example, the fixed and jittered-standard protocols can be applied at 40% deviance. In order to counterbalance the order of recoding the two protocols, it is preferable to use two sessions. The obtained data point can be evaluated with respect to a graph plotting the fixed MMN as a function of the jittered MMN for 40% deviance (figure 5, middle). Significant deviations from the regression line obtained for the normal population point to a deficit in the regularity detection mechanism.

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Figure 1.

Grand average responses. A–C: Grand average responses as measured at electrode Fz ($n=19$) for each of the six conditions (response of each subject is averaged over the two measurements; see Methods) A: Responses to the standard; 1000 Hz for fixed standard conditions; average of the nine responses to the 1000 Hz $\pm 2\%$ range in the jittered standard conditions. B: Responses to the deviants. C: MMN difference waves (Dev–Standard) for fixed standard conditions; (Dev–averaged nine responses) for jittered standard conditions. D: Grand average responses ($n=22$) under the 40% deviance condition to 1000 Hz in the fixed standard protocol (solid line), to 1000 Hz in the jittered standard protocol (dashed line), and to 980 Hz in the jittered standard protocol (dotted line). The 980-Hz mini standard is the most distant standard and is therefore expected to be the least adapted one. Vertical dotted lines indicate the intervals during which the average MMN deviated from zero (see C).

Figure 2.

The jitter effect and its interaction with the degree of deviance. Cross-subject average difference waves were calculated by subtracting the jittered ERPs from the fixed ERPs for A: standard (1000 Hz; average across nine frequencies), B: deviant, and C: MMN for each individual and then averaging across subjects separately for each deviance condition. Error bars indicate cross subject standard error. The vertical dashed lines indicate the intervals during which the average MMN deviated from zero (see Figure 1C). The vertical solid lines indicate the peak amplitudes of the jitter effect, demonstrating similar peak latencies of the jitter effects calculated for the responses to deviants and for the MMN waves.

Figure 3.

Scalp distribution of the grand average MMN waves. Right: Grand average MMN waves ($n=19$) obtained under the fixed standard (solid line) and the jittered standard (dashed line) protocols presented for the 8% (upper part) and 40% (lower part) deviance conditions. Three frontal (F3, F4, Fz), one central (Cz), and two mastoid (M1, M2) electrodes are presented (see Baldeweg et al., 2002). Recordings are re-referenced to the nose electrode. MMN waves are inverted at the mastoids, as expected. The distribution of the jittered MMN versus the fixed MMN is very similar. Left: Topographic voltage distribution maps of 8% MMN (upper part) and 40% MMN (lower part) during a time window of 100 to 250 ms are presented. For each deviance condition fixed MMN, jittered MMN and jittered effect distributions are shown. The time window is parsed into 50-ms intervals, three rows for each condition.

Figure 4.

Test-retest Pearson correlations between MMN peak amplitudes measured in the first versus second assessment of the same deviance condition. Each symbol denotes the peaks of one participant. A: Fixed standard protocol. B: Jittered standard protocol. The diagonal shows 1:1 relations between test and retest.

Figure 5.

The MMN jitter effect at the level of single subjects. MMN peak amplitudes under the jittered versus the fixed standard protocol, plotted for each participant, for each of the three deviance conditions. Peaks of each participant were computed by averaging the peaks of the two assessments administered under each condition. Dots under the diagonal denote smaller MMN responses under the jittered than under the fixed standard protocol.

Figure 6.

The magnitude and dynamics of adaptation and rule violation detection, plotted separately (electrode Fz). A: Grand average of the jittered MMN recorded under 8% (left), 40% (middle), and 100% (right) deviants, respectively (replot of data presented in Figure 1), reflecting adaptation mechanisms. B: Grand average of the jitter effect (n=19), that is, the difference between the jittered deviant and the fixed deviant at 8%, 40%, and 100% deviance (replot of data presented in Figure 2), reflecting mechanisms of rule violation detection. The dashed vertical lines mark the peaks of the plotted waves and indicate simultaneity of the jittered MMN and jitter effect.