UNIVERSIDADE FEDERAL DE MINAS GERAIS

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IS THE MISMATCH NEGATIVITY A SYMMETRICAL MEASURE OF CHANGE?

MATHEMATICO-PHILOSOPHICAL AND EXPERIMENTAL INVESTIGATIONS AIMED AT MAPPING PSYCHOTOPOLOGIES

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M. S. Thesis presented to the Universidade Federal de Minas Gerais for the title of Master in Neuroscience

Concentration area: Psychophysics

Advisor: Prof. Dr. Hani Camille Yehia

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RESUMO

FREIRE, IL. Será a Negatividade do desviante (*Mismatch Negativity,* MMN) uma medida simétrica de mudança? Investigações matemático-filosóficas e experimentais dirigidas ao mapeamento de psicotopologias. Belo Horizonte. Departamento de Neurociências, Universidade Federal de Minas Gerais, 2010. 58 p. Dissertação de Mestrado em Neurociências.

O potencial evocado conhecido como *Negatividade do Desviante* (*Mismatch Negativity,* MMN) é uma medida psicofísica de mudança discriminável. A forma mais simples de evocá-lo é através de experimentos no paradigma da *bolota estranha* no qual dois estímulos são apresentados em alternância aleatória: um deles acontecendo mais frequentemente, chamado de *padrão,* e outro acontecendo mais raramente, chamado de *desviante.* O MMN é a forma de onda calculada como a subtração da resposta ao padrão da resposta ao desviante. A literatura caracteriza o MMN como uma forma de onda cuja amplitude do pico aumenta e latência do pico diminui tanto com decrementos em probabilidade de apresentação do desviante quanto com a "diferença" entre estímulos utilizados nos papéis de padrão e desviante. Tal caractarização do MMN é em essência incompleta, já que não determina como fazer essa medida da "diferença" entre estímulos padrão e desviante, e as possibilidades de escolha de espaços métricos para o domínio dos estímulos físicos são várias. A literatura comumente assume que o MMN é uma medida simétrica de mudança e que uma reversão de papéis de padrão e desviante para os estímulos físicos utilizados no experimento da bolota estranha não afetaria a forma de onda do MMN. Diferenças observadas entre MMN's obtidos no par de experimentos determinados pela troca de papéis são, na literatura, explicadas por diferenças em outros potenciais evocados sendo gravados durante o experimento. Este texto mostra que a hipótese de simetria do MMN é mal-definida, faltando-lhe rigor matemático, e propõe um paradigma experimental para a investigação da questão da simetria do MMN sob determinado espaço métrico para os estímulos físicos. Em termos experimentais, é demonstrado que o MMN para frequências se comporta de forma assimétrica sob a métrica "diferença absoluta, em Hertz, entre a frequência fundamental de tons complexos de três hamônicos". Se for admitida a hipótese de que o MMN seja, em essência, uma medida simétrica de mudança, então a busca por espaços métricos para estímulos, sob os quais o MMN se comporte como tal, pode ser utilizada como ferramenta para o mapeamento da *psicotopologia* do processamento daquele tipo de estímulo.

Palavras-chave: potenciais relacionados a eventos, Negatividade do Desviante, ciência cognitive, métrica de distância, métrica de distorção, psicotopologia, psicoacústica, psicofísica, representação mental

ABSTRACT

FREIRE, IL Is the Mismatch Negativity a symmetrical measure of change? Mathematico-philosophical and experimental investigations aimed at mapping psychotopologies. Belo Horizonte. Neuroscience department, Universidade Federal de Minas Gerais, 2010. 58 p. Dissertação de Mestrado em Neurociências.

The event-related potential known as the *Mismatch Negtivity* (MMN) is a psychophysical measure of discriminable change. It is most simply evoked through experiments in the oddball paradigm, in which two stimuli are presented in random alternation, one more happening more frequently, thereby called the *standard*, and another more rarely, thereby called the *deviant*. The MMN is the waveform computed as the subtraction of the response to the standard from the response to the deviant. The literature characterizes the MMN as a waveform whose peak amplitude increases and peak latency decreases with decrements in the probability of presentation of deviant and with the “difference” between standard and deviant stimuli. This characterization of the MMN is in its essence incomplete, as it does not determine how to measure the “difference” between standard and deviant stimuli, and many metric spaces can be used for the domain of physical stimuli. The literature commonly assumes that the MMN is a symmetrical measure of change and that reversing roles of standard and deviant for the physical stimuli employed in the experiments will not affect the MMN. Differences observed between the MMN’s obtained in the pair of experiments determined by the swapping of roles have been explained by differences in other event-related potentials being recorded in the experiments. This work shows that the MMN symmetry assumption is ill-defined, lacking in mathematical rigour, and proposes an experimental framework for cleanly investigating whether the MMN behaves as a symmetrical measure of change under a given metric for the space of physical stimuli. Furthermore, experimental results for the frequency MMN, under the metric “absolute value of difference, in Hertz, between the fundamental frequency of three-harmonics complex tones”, are presented, and it is shown that, in this metric space for physical stimuli, the MMN is an asymmetrical measure of change. If it is assumed, *a priori*, that the MMN is a symmetrical measure of change, then searching for metric spaces for physical stimuli, under which the MMN behaves as such, can be used as a tool for mapping the *psychotopology* of processing that sort of stimuli.

Keywords: event-related potentials, Mismatch Negativity, cognitive science, distance metric, distortion metric, psychotopology, psychoacoustics, psychophysics, mental representations

LIST OF ILLUSTRATIONS

List of Symbols and definitions

ϕ. Phi. The domain of physical events.

χ. Chi. In the Greek alphabet, χ comes right after ϕ and right before ψ. In this text it refers to the domain of the Mismatch Negativity, overriding any traditional meaning.

ψ. Psi. The domain of mental events.

$\Re$. The set of real numbers.

C(n, p). Number of different p-combinations of an n-element set. Its value is

$$C(n, p) = C_n^p = \frac{n!}{(n-p)!\,p!}$$

cMMN. "Classical" MMN, defined, in the *oddball paradigm*, as ERP for standard subtracted from ERP for deviant. Standards and deviants are presented within the same experimental block, in contrast against each other.

Cohen's d. a.k.a. **d'** *("d-prime")*. Effect size measure, for quantifying the strength of the difference from sample P_1 to sample P_2, with sample means μ_1 and μ_2, sample standard deviations σ_1 and σ_2, and sample sizes n_1 and n_2. It measures the difference between the sample means in units of pooled standard deviations:

$$d' = \frac{\mu_1 - \mu_2}{\sigma_{pooled}}, \text{ where}$$

$$\sigma_{pooled} = \sqrt{\frac{(n_1-1)\sigma_1^2 + (n_2-1)\sigma_2^2}{n_1+n_2}}$$

d'. See Cohen's d.

Distance metric. A distance metric on a set X is a function $M : X \times X \to \Re$, satisfying $\forall x,y,z \in X$,

1. $d(x, y) \geq 0$ (non-negativity)
2. $d(x, y) = 0 \Leftrightarrow x = y$ (identity of indiscernibles)
3. $d(x, y) = d(y, x)$ (symmetry)
4. $d(x, z) \geq d(x, y) + d(y, z)$ (triangle inequality)

If the third requirement (symmetry) is dropped (keeping 1, 2, and 4), then the function is called a distortion metric.

Distortion metric. See *distance metric.*

EEG. Electroencephalogram.

EMR. Electromagnetic radiation.

ERP. Event-related potential.

MMN. see cMMN.

N100. Negative-going ERP, peaking at 80-120 ms of stimulus onset. It is elicited by any unpredictable stimulus. Its amplitude shows refractoriness upon repetition of a stimulus. The use of a ramp of intensity at tone onset decreases the N100 (Spreng 1980).

Oddball paradigm. Experimental paradigm in which two different stimuli are presented in random alternation. One of the stimuli happens significantly more rarely than the other and is thus called the *oddball*, or *deviant,* while the other one is called the *standard.*

pMMN. "Pure" MMN, defined, in the oddball paradigm, as ERP for a stimulus ϕ_1 presented as standard minus ERP for that same ϕ_1 presented as deviant. Two experimental blocks are required for computing a pMMN. Probability of deviant should be the same in both blocks, as well as the numeriacal value of the metric function from standard to deviant.

$pMMN_H$. The pMMN derived for the higher-frequency tone, in the oddball paradigm for frequency MMN, assuming a distance metric in ϕ.

$pMMN_L$. The pMMN derived for the lower-frequency tone, in the oddball paradigm for frequency MMN, assuming a distance metric in ϕ.

ppMMN. A set of two MMN's for which the numerical value of the metric function from standard to deviant is the same, as is the deviant probability.

SOA. Stimulus onset asynchrony. The time interval between the onsets of two consecutive stimuli.

TABLE OF CONTENTS

INTRODUCTION

This text is an exposition of experiments and theoretical work developed in the area of psychophysics, which is, in general, aimed at understanding the relationship between physical stimuli and psychological sensations. Measuring "psychological sensation" can only be done indirectly, either through language, behavioral experiments, or physiological correlates.

Psychophysics is about measuring "psychological sensation" through physiological correlates, from visible signs like the degree of dilation of pupils and presence of goosebumps, to quantities requiring measurement machinery, like the conductivity of the skin, measured by a galvanometer, or the timecourse of shifts in differences of potentials on the skull surface, which reflect current dipoles inside the brain, and are measured by the electroencephalogram (EEG).

The last century has seen the popularization of EEG technology, and research with *event related potentials* (ERP's) has boomed. ERP's are EEG waveforms that are related to current dipoles involved in the processing of a *triggering event*, which may be exogenous, like a clarinet note, or endogenous, like the imagination of the movement of a finger[1].

The psychophysical measure taken as a tool for experimentation and also as an object of study in itself is the *Mismatch Negativity* (MMN). The MMN is an ERP measure of discriminable change, most simply evoked through experiments following the *oddball paradigm,* in which two types of stimuli are presented in random alternation, one happening more frequently and another happening more rarely. The MMN's peak amplitude and latency parameters are functions of stimulus unpredictability within a context, known to vary with both the probability and the magnitude of change.

Experimental work was conducted in the auditory modality, with the frequency MMN, *i.e.*, an MMN evoked by differences in the frequency of the two types of stimuli utilized in the experiment. The motivating question was: how is perception of **magnitude of change** related to **direction of change**? That is, how is magnitude of change sensed when perceiving one extraneous stimulus, in the special case of this work, a G3 sinusoidal tone, among many

[1] Exogenous events are of course perceived in the context of a brain-state, and therefore have endogenous counterparts.

exemplars of another type of stimulus, here A4 sinusoidal tones, as compared to a situation in which roles of the physical stimuli were swapped, that is, when A4 appears against a G3 background. The literature traditionally assumes that the MMN waveform will be the same in both cases, and that any deviation from this would be due to contamination of the computed MMN curve by other event-related potentials. A recent paper by Colin et al. (2009) found an effect of direction of change in the MMN curve, utilizing duration MMN's, and reports the finding as a surprise:

> The present report stems from observations made during a study of MMN parameters across a wide range of duration contrasts. The data accumulated up to now strongly suggested that there was an unanticipated systematic amplitude difference between MMN's evoked by shorter vs. longer deviants. The data analysis reported here was performed in order to verify the serendipitous finding of an effect of deviance direction on the MMN parameters, an issue that has hardly been addressed in the literature.

Colin et al. (2009) offer an explanation to the effect they found, which is particular to the duration MMN case[2]. In this dissertation, though, a different approach is taken to discussion of the asymmetry of the MMN curve regarding deviance direction: in Chapter 3, a purely theoretical study discusses how to define metrics in different spaces: the space of physical stimuli, ϕ; the space of psychological sensations, ψ, and the space of the parameters of the MMN waveform. As such, we conclude that defining a "reverse" experiment in which both the probability of deviance and the metric from standard to deviant is kept the same, is not as simple as switching which stimuli is in the role of a background, or standard, and which stimuli is in the role of the foreground, or deviant, but depends on various assumptions about the nature of metric spaces.

The text is organized as follows:

Chapter 1**, Psychophysics,** is a somewhat personal account on psychophysics. It is written in an informal style, like that of popular science books, with the occasional obscurely stated reflections. In case the reader wishes to skip it, he will find that any concepts or nomenclature

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[2] This explanation is presented on Chapter 6, *Discussion*.

thereby introduced, if needed for an understanding of the scientific work, have been soberly catalogued in the List of Symbols.

Chapter 2, **Background,** discourses on electroencephalograms, event-related potentials, and, finally, the mismatch negativity (MMN).

Chapter 3, **Experimentation,** is a detailed description of the experimental work that was performed. It's the arts & crafts, nuts & bolts, chapter.

Chapter 4, **Results,** is a description of the data obtained through the work described in the previous chapter.

Chapter 5, **Discussion,** reviews current MMN literature in light of the ideas hereby developed and of data presented in the previous chapter. In particular, section 5.4, **A novel, more rigorous formalization of properties of the Mismatch Negativity,** may be the most interesting contribution of the dissertation. Trying to apply mathematical rigour to an apparently straightforward verbal construction utilized in the conceptualization of the MMN proposed by Näätänen in 1990, and still widely accepted until today, gives rise to a few interesting complications, to an improved paradigm for measuring the MMN, and to a theoretically-determined critical discussion of some results from the published literature.

Chapter 6**, Conclusions,** enumerates conclusions drawn from the experimental work.

Appendix, **Validation of experimental environment,** presents demonstrations of the correct working of the experiments, including the balloon sessions, in which we tried to measure evoked potentials from balloons so as to assure no data contamination was polluting our results.

CHAPTER 1. PSYCHOPHYSICS

According to (Gescheider, 1997), "psychophysics consists primarily of investigating the relationships between sensations in the psychological domain ψ and stimuli in the physical domain ϕ."

The techniques for measuring events in ϕ are relatively well-developed, thanks to a long-standing, well-justified obsession of physicists, expressed by Galileo Galilei as "Measure what can be measured, and make measurable what cannot be measured."

But would an expenditure of effort in trying to assess and measure events in ψ, through new methodological and technological means, be justified? The uses would be many: understanding communication by correlating mental events in ψ with characteristics in ϕ of communicative acts; for neurology and psychiatry, establishing correlates in ϕ – either as causes or as consequences – of mental states in ψ, or for evaluating the mental faculties of uncommunicative patients, like those in a comatose state, or newborns; for criminalistics (recall the polygraph, aka "lie detector", incidentally but too amusingly celebrated in literature in the self-baptism of the dog-turned-human *Poligraf Poligrafovich Sharikov* (Mikhail Bulgakov, *Heart of a dog,* 1925/1998)); for linguistics[3]; for an understanding of how various elements of music are perceived, how music can be semantically interpreted and how it can exert such a deep effect on people's emotional states; and even back to physics: Henri Poincaré, in his (1905/2001) book *On the value of science*, begins the chapter *On the measure of time*, with the sentence "So long as we don't go outside the domain of consciousness, the notion of time is relatively clear."

That chapter of Poincaré has quite a few considerations on psychophysics, he even puts forth a question about the sense of time, which has been extensively investigated through experiments with evoked potentials (Jones 2002, Chen *et al.* 2010, Roger *et al.* 2009, Pulvermüller *et al.* 2006, etc)

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[3] Defining language events as belonging to either ϕ or ψ is trying. The channel is in ϕ but the source and destination, in a self-contained level of abstraction, can more easily be modeled in ψ, though without exclusion of a lower level in ϕ.

> Can we transform psychologic time, which is qualitative, into a quantitative time? […] This difficulty has long been noticed; it has been the subject of long discussions and one may say the question is settled. We have not a direct intuition of the equality of two intervals of time. The persons who believe they posses this intuition are dupes of an illusion. When I say, from noon to one the same time passes as from two to three, what meaning has this affirmation? (Poincaré, 1905).

Lastly, the relationship between the domains ψ and ϕ is one of the grails of philosophy.

Quantifying events in ψ is not always easy[4] – but it's often tempting. Let's delay the text about the perception of differences in piano tones, from G3 to A4, versus in the opposite direction from A4 to G3, to the next section, as ψ and ϕ can be so much more than that. For now, take love: in which sense could the difference between the love of one couple and that of another be only quantitative, a matter of which and how many adverbs, in which order, are chained between the words "I love you" and "much"? This silly idea probably calls for some sort of decomposition of "love" into components, but, the bottom question is, could such things ultimately be measured? What is measured by the exact frequency and angle at which a german shepherd wags her tail[5], by the exact frequency, speed and pressure employed when she licks your face, or how watchfully she behaves from far away whenever a stranger approaches you: how quietly she holds her breath (with the tip of her tongue dangling out of her quasi-closed mouth), how fixedly she stares, and how sharply she points her ears; what if that happens p% of the times a stranger comes near, and in the other (100 – p)% she does not take notice because she is busy with something else? What is measured by your reaction time for jumping after that dog when she's a meter away from a coiled snake, catching her in your arms and jumping away? Aren't those numbers enough to measure the love[6]? More directly, Umberto Eco, in *The name of the rose* (1980/1983), cites Avicenna, the Persian sage, and Galen, the Roman physician:

> Avicenna advised an infallible method already proposed by Galen for discovering whether someone is in love: grasp the wrist of the sufferer and utter many names of

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4 Oh and who can we turn to in this need? Not angels not people and the cunning animals realize at once that we aren't especially at home in the deciphered world (Rainer Maria Rilke, Duino Elegies, (1912/2006))

5 As a matter of fact, dogs wag their whole body.

6 The focus on dogs on this digression on psychophysics probably comes from the fact that dogs do not speak, and this forces the dog-human love and friendship bond to be created on the basis of ϕ about ψ.

> members of the opposite sex, until you discover which name makes the pulse accelerate.

so a function of rate of heartbeat, in ϕ, would be a measure of love, in ψ, and the manner advocated to take that measure would be through language. That is psychophysics as well!

A famous example is Libet's (1999) event-related potential study of free will.

An interesting question to be posed once one decides that some of the more abstract members of ψ can be quantified, would be: what's the interplay of the quantitative and the qualitative in the domain of ψ? Could important qualitative changes occur in ψ upon reaching quantitative thresholds? An example of such is described in Milan Kundera's *Eduard and God* (1969/1999):

> Eduard is sitting in a wooden pew and feeling sad at the thought that God does not exist. But just at this moment his sadness is so great that suddenly from its depth emerges the genuine living face of God. Look! It's true! Eduard is smiling! He is smiling, and his smile is happy. Please keep him in your memory with this smile.

But… this is too far gone on thoughts on quantities, measurements, ψ, qualitative transitions, even God, ϕ, magnitudes of feelings, Olympics with babies, snakes, far-away olfactory feats, and what not, pardon me and my digressions on psychophysics: the real problem now is that the rest of this thesis is going to be mind-numbingly boring, and at points irritating, except for a minorly amusing corollary about the absence of event-related potentials in balloons, which was based on necessary work to prove that we were actually measuring evoked potentials instead of artifactual noise. Evoked potentials are hard to measure, because their magnitude is on the order of μvolts, and it was a lot of work to make sure that all the equipment was functioning properly. The grey balloon sessions were left for an Appendix. The rest of the text is about the correct manner of measuring the workings of a neural system that is considered an EEG correlate of discriminable change, outputting an EEG waveform that peaks within 90 to 200 ms of change onset, the *Mismatch Negativity* (MMN).

CHAPTER 2. BACKGROUND

2.1. THE ELECTROENCEPHALOGRAM AND EVENT-RELATED POTENTIALS[7]

Electrical currents in the brain are associated with net differences of potential on the skull surface. Measurements of these differences of potential over time make up the *electroencephalogram* (EEG).

The first EEG was measured in 1875, on the exposed cortex of rabbits and monkeys, by Richard Caton, in England. Caton was able to observe both spontaneous electrical activity and sensory *event-related potentials* (ERP's) (Swartz and Goldensohn, 1998).

An ERP to a triggering event *e* is the set of changes in the EEG that are caused by *e*. The timecourse of known ERP's is on scales of tens to hundreds of milliseconds.

A schematic illustration of auditory ERP's is shown in Figure 2.1: in the first 10ms following stimulus onset, very specific waveforms are drawn in the EEG due to currents flowing at the brainstem level; in the other end of the time and hierarchy of processing spectrum, the P300 appears, with latencies of more than 300 ms of stimulus onset, as an EEG correlate of processing of a rare, task-relevant stimulus (Duncan et al., 2009). Brainstem-level ERP's are naturally easier to discover and characterize. It's interesting, though, that current research has identified cortical responses like the N400. The N400 exists in the domain of language processing, and its amplitude is correlated with how surprising is the appearance of a word in a given context! (Lau et al., 2008).

One is urged to notice that the voltage fluctuations between certain pairs of points on the skull surface draw very particular EEG waveforms in response to certain events, upon repetition of events in this class to an experimental subject and even across different subjects. This is not shocking if one considers the current state of knowledge of functional neuroanatomy, with precise localization of some functions to known brain structures, especially of lower-level functions in sensory processing. For the justifiably skeptical reader, the inter-subject stability and

[7] Some authors distinguish "evoked potentials" from "event-related potentials" on the basis of whether they appear as results of lower-level sensory processing or of cognitive, context-dependent, cortically-based, task processing, respectively. In this text the terms are used interchangeably.

test-retest replicability of auditory event-related potentials N1 and P2 have been demonstrated in Roth et al., (1975) and Shelley et al. (1991).

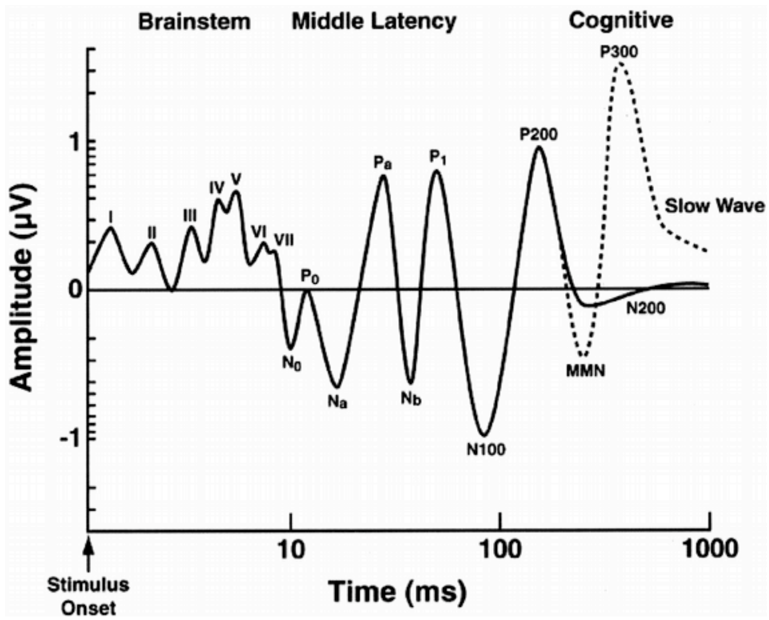

Figure 2.1. Schematic illustration of auditory evoked potentials. Logarithmic scales are used for amplitude and latency. Figure extracted from Picton et al. (1974).

ERP changes are of course embedded in the overall spontaneous activity of the brain. EEG differences of potential, when measured on the skull surface, are on the order of hundreds of millivolts, while ERP's are on the order of a few microvolts. This makes appropriate experimental design and signal processing techniques necessary to isolate ERP's from other activity being measured in the EEG. The most common *modus operandi* of ERP research nowadays is experimental design based on repeated presentation of the stimulus that triggers the ERP and signal processing by time-locked, stimulus-synchronized, EEG averaging to cancel out non-specific brain activity. Other issues are involved, mainly regarding data de-noising, but such are peripheral to the basic understanding of the concept and will not be discussed here. A good introductory book on ERP research is (Luck, 2005).

2.2. THE MISMATCH NEGATIVITY

The Mismatch Negativity (MMN) is an event-related potential whose latency and amplitude parameters are commonly taken as psychophysical indexes of discriminable change. They are measures of the brain's response to violations of a rule, established by a sequence of sensory stimuli (Näätänen, 1992). The MMN can be most simply evoked through the *oddball paradigm,* in which *standard* and *deviant* stimuli are presented in random alternation, with the probability of presentation of standard being higher than that for the deviant. One example of experimental design following the oddball paradigm is presentation of randomly alternating middle C and middle F piano tones, each occurring with probabilities 85 and 15%, respectively. The MMN would then be defined as the subtraction of the potential evoked by the C tone from the potential evoked by the F tone. The waveform peaks between 90 and 200 ms after stimulus onset, depending on the type of regularity that is broken, and lasts between 80 and 200 ms (Kujala et al., 2007).

The MMN was discovered in 1978 at the Institute for Perception, TNO, The Netherlands (Näätänen, Gaillard, Mantysalo, 1978). As of February 14th, 2010, a Pubmed search for "mismatch negativity" retrieves 1264 articles, spanning diverse research and application areas such as sensory processing, clinical neurology and psychiatry, linguistics, phonoaudiology, neuropharmacology, and memory and attention functions.

In Näätänen (1990, 1992), the folllowing properties are given for the MMN:

I. The smaller the probability of occurrence of the deviant within the sound sequence, the larger the MMN's amplitude.
II. The larger the difference between deviant and standard stimuli, the larger the MMN's amplitude, and the shorter its peak latency.
III. The MMN is elicited whether the subjects are instructed to detect the deviant sounds or are engaged in a neutral primary task (e.g., reading a book). In the first case, though, the waveform is overlapped by attention- and task-dependent components, such as the P165 and the N2b (see, e.g., Sams, Paavilainen, Alho, & Näätänen, 1985).

Interestingly, the MMN appears also for violations of abstract rules, like "the higher the frequency of a stimulus, the louder its intensity", and, as such, it must rely on mechanisms for detecting this sort of perceptual invariance (Paavilainen et al., 2003).

2.2.1. A recent paradigm improvement for computing the Mismatch Negativity

This subsection explains a paradigm aimed at better measuring the MMN, presented in (Kujala et al., (2007)[8,9]. Special mention is made of this idea because it's a seed for the developments made in the work presented in this dissertation.

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[8] (Kujala et al., 2007) is actually a review, but no citation of an original source was found in the published text.

The paradigm aims at eliminating, from the MMN curve, the non-MMN effects that are due to different physical characteristics of standard and deviant stimuli. In an oddball paradigm experiment, in which physical stimuli ϕ_1 and ϕ_2 are presented, respectively, as standard and deviant, with deviant probability p, one subtracts from the ERP to ϕ_1 presented as deviant, not the ERP to ϕ_2 presented as standard, as is classically done, but an ERP to ϕ_1 presented as standard. There are two options for choice of this last mentioned ERP: either take an ERP to ϕ_1 presented by itself, or an ERP to ϕ_1 presented as standard against ϕ_1 presented as deviant with probability p (i.e., run an experiment in the oddball paradigm in which standard/deviant roles for ϕ_1 and ϕ_2 are reversed). The MMN calculated in this manner will be called a *pure MMN,* or *pMMN.* In the second approach, two pMMN's are obtained, and collectively called a *pair of pMMN's,* or *ppMMN*. The second approach is illustrated in Figure 2.2.

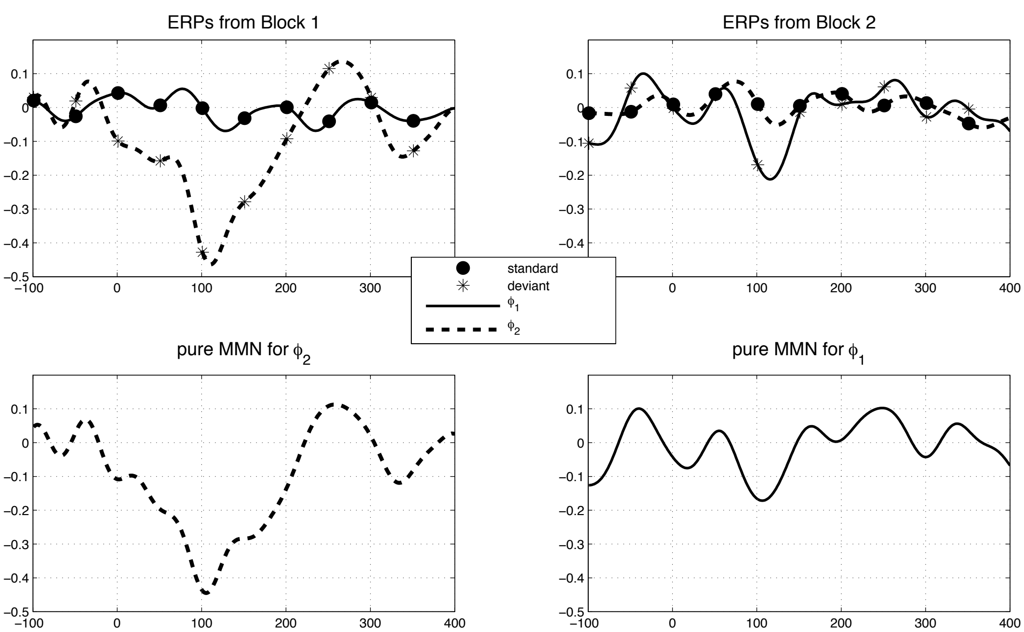

Figure 2.2. The "pure" MMN. In block 1, ϕ_1 is presented as deviant and ϕ_2 is presented as standard. In block 2, roles are reversed. ERP's derived during presentation of ϕ_1 are drawn in broken lines, and, during presentation of ϕ_2, in full lines. Standards are marked 'o' and deviants are marked '*'. A "pure" MMN is calculated as the subtraction of ERP for ϕ_i presented as standard from ERP for ϕ_i presented as deviant. Deviant probability is the same in both blocks. The figure shows real data obtained in our lab with the frequency MMN.

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[9]The text from the relevant section of (Kujala et al., 2007) has been transcribed in Box 5.2 of this dissertation.

CHAPTER 3. EXPERIMENTATION

This chapter describes all aspects of the experimental work: from creation of stimuli to the set up of the data recording environment and signal processing techniques.

Closely related to this chapter is the Appendix, which provides a demonstration of absence of data contamination by experimental artifacts: all procedures were repeated on an inflated balloon in the place of a live-brain-filled skull. Artifacts can lurk in from unexpected sources.

3.1. EXPERIMENTAL SESSIONS

3.1.1. EXPERIMENTAL SUBJECTS

EEG data was collected from 7 adult subjects, aged between 20 and 30 years old, recruited among graduate students at UFMG. None of the subjects was ever diagnosed with any auditive, neurological, or psychiatric disorder, neither made use of any medicament that could interfere with the generalization of the results to a healthy population. The subjects were naïve about the purpose of the study.

3.1.2. STIMULI

Stimuli were 200 ms tones of 196.0 Hz (called t0 from now on) and 466.2 Hz (called t1 from now on), each added of their first two harmonics, with linear onset and offset ramps of 10 milliseconds each. Choice of fundamental frequencies was based on Fujioka, Trainor and Ross, (2008), and the use of complex tones with extra harmonic was based on Jones, (2002) and Novitski et al., (2004). Harmonical tones elicit MMN with shorter latencies and larger amplitudes than do pure sinusoidal tones. Stimulus onset asynchrony (SOA) was 500 milliseconds. Probability of deviant was 15%, and deviants were presented in random order, under the condition that no two consecutive deviants were allowed. 1800 trials were run in each round, and in-between rounds there was a period of one minute of silence. For 3 of the subjects, 2 rounds were presented: in the first round, the standard was the 196 Hz tone, and the deviant was the 466.2 Hz tone. In the second round, roles were reversed. For 4 of the subjects, a third round was presented which exactly reproduced the first round. The sequence of standards and deviants was the same in all rounds, what varied was only which tone was allocated to the role of standard or deviant. A third round was introduced to control for experimental artifacts that could be introduced due to ordering of presentation. Stimuli were played as .wav files by iTunes 9.0.2 software on a MacBook running 10.5.8 OS X. The method of stimulus delivery was shown to yield accurate timing. The demonstration is described in the Appendix.

3.1.3. The data collection environment

A schematic of the wiring of machinery for data collection is shown in Figure 3.1.

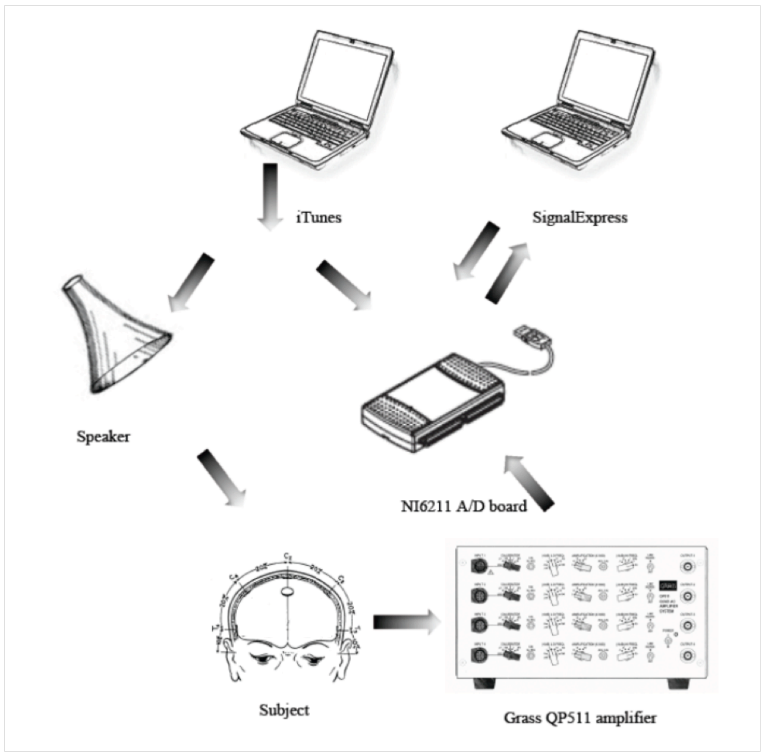

Figure 3.1. Schematic of the data collection environment. Subject's head should be kept as far as possible from all power cables and electronics. The speaker and amplifier utilized A/C power, all other machinery utilized D/C power. Regardless of utilizing A/C or D/C power, computer monitors can emit significant electromagnetic radiation (EMR) at the screen refresh ratio. Headphones can be a source of EMR as well, and the utilization of a speaker provides a solution to this problem, which is made more convenient if performing the experiments in an acoustically shielded room. Before running each experiment, it's a good idea to check proper functioning of machinery by briefly displaying cardiac signals on the live screen[10].

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[10] For quickly and conveniently acquiring cardiac signals, place the ground electrode on the back of your right leg and hold it there by flexing the knee. Hold, with the right hand, one of the other two electrodes by your right shoulder, and, with the left hand, the other electrode in front of your heart. No conductive paste is needed.

Voltage was measured between Fz (that is, at one-third of the shortest path on the skull surface from nasion to inion) and the right mastoid, using a Grass QP511 amplifier system. Ground potential was established at the subject's forehead. Analog filtering was performed in the QP511 system, with band-pass filtering between 0.1 and 100 Hz and line filter at 60 Hz. Signal was amplified by a factor of 50K. The amplifier system's power was supplied by the building's power lines.

Measurements were made using gold electrodes after skin cleansing (with alcohol). Conductive paste was applied between the electrodes and the skin. The subject was kept at least one meter away from any electricity-conducting cable or working electric equipment, such as the laptops or the amplifier system.

Experiments were run in an acoustically shielded room. Stimuli were delivered by speakers placed 1.5 meters away from subject's ears; sound intensity at the ears was 70dB SPL. Subjects were instructed to lie down, relax and listen passively to the stimuli with their eyes open. Light intensity was kept low.

Analog-to-digital conversion was performed by a National Instruments NI6211 acquisition board, and controlled by the software NI LabVIEW SignalExpress, running on a Windows Vista laptop. The power to the acquisition board was supplied via a USB cable connected to this same laptop. The laptop was run on batteries. The acquisition board was configured to sample the signal at 1kHz and acquire the EEG data in referential mode.

The acquisition board also performed on-the-fly low-pass filtering of the EEG signal at 40Hz by a sixth order Butterworth filter, which was used for single purpose of real-time visualization. Epochs were visualized two at a time, and the image was fully refreshed with 2 new epochs every second, in the same display on which the acquired stimulus was also shown, in a synchronized manner.

The stimuli were delivered to the acquisition board and then to LabVIEW Signal Express, via splitting the sound output from the laptop between the speakers and the acquisition board. Stimuli were also recorded, on referential mode, with ground set at the board's own ground.

The raw EEG signal, as output by the amplifier system, and the recorded stimuli were saved as comma-separated values (.csv) files which were later analysed by custom-made Matlab scripts, to be discussed in the next subsection.

3.2. SIGNAL PROCESSING

Epochs were 500ms long, formed by the period of 100ms before stimulus onset and the period of 400 ms after stimulus onset. The signal was low-pass filtered at 40 Hz, by a Butterworth filter of 8th order. This filtering was performed in accordance with the fact that the MMN's carrier frequency is below 35 Hz (Sabri & Campbell, 2002). Each epoch was baseline-corrected by subtracting its mean amplitude in the 100ms pre-stimulus interval from each sample. Epoch rejection was performed automatically (some authors as Luck (2005) recommend a second pass, in which epochs are removed by visual inspection but here we preferred to avoid this procedure due to its subjective nature), eliminating epochs in which more than 2% of samples were above a threshold value of 0.1 V. MMN typically peaks at around 0.2 microvolts. Subjects for which more than 50% of epochs were rejected, in either of the two blocks, were eliminated from further analyses[11].

3.3. VALIDATION OF EXPERIMENTAL SETUP AGAINST ARTIFACTUAL DATA CONTAMINATION

Validation of the experimental setup against various possibilities of artifactual data contamination was performed by repeating all data collection procedures using an inflated balloon in place of the experimental subjects' skull, and then analyzing the data so collected by the same signal processing routines used for the EEG data. Results of these experiments are described in the Appendix[12].

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[11] Signal-to-noise ratio is given by the variance of the ERP constituent, divided by the variance of the noise constituent, SNR = var(signal) / var(noise). Assuming the noise to be random, the SNR is expected to improve with the square root of the number of averaged trials. The subject rejection method described above is not only aimed at keeping a minimum SNR per subject by ensuring a minimum number of valid epochs entering the averaging process, as with 50% of trials removed, if no other experimental conditions are dependent on the number of trials removed, we'd still be left with 70% of the SNR (Luck, 2005). The important point is that a large ratio of removed trials indicates bad experimental conditions, pointing to rejection of the whole experimental session, due either to recording mistakes or to behavior of the subject.

[12] The first time I used the air-filled balloon head, I found "evoked potentials" which I later discovered were being caused by the headphones. The "evoked potentials" disappeared once I switched to the speaker setup.

CHAPTER 4. RESULTS

Experiments and signal pre-processing were performed as described in the previous chapter, *Experimentation*. This chapter presents the results of application of methodology, organized in various figures and numerical measurements.

The chapter is organized as follows:

Section 4.1, ***Streaming data,*** presents the results of the methodology applied to signal acquisition, and displays recordings of streaming data.

Section 4.2, ***Single trials***, shows what a single trial looks like after application of filters and baseline correction, and gives results of application of epoch rejection procedures.

Section 4.3, ***Analysis of evoked potentials,*** is divided into two subsections:

> Section 4.3.1, ***Averaged waveforms,*** shows averaged waveforms and tables with numerical values for their peak latencies and amplitudes. The ERP's described in this subsection are: ERP's for each (tone, condition), e.g., (high, deviant); cMMN; pMMN. Averages include both grand-averages and intra-subject averages.
>
> Section 4.3.2, ***MMN's under sample analysis,*** presents statistical analysis of differences between the ERP's for deviants and the ERP's for standards, for each subject. The sets of samples being compared are chosen according to using the cMMN or the pMMN. Comparisons rely on the t-test and on the effect size measure known as *Cohen's d,* or *d'*.

4.1. STREAMING DATA

An experimental session lasting 15 minutes is depicted on Figure 4.1. Both EEG and stimuli data are displayed in two time-aligned plots. Figure 4.2 zooms into a 3-second interval of figure 4.1, displaying the presentation of 6 epochs and their respective EEG responses.

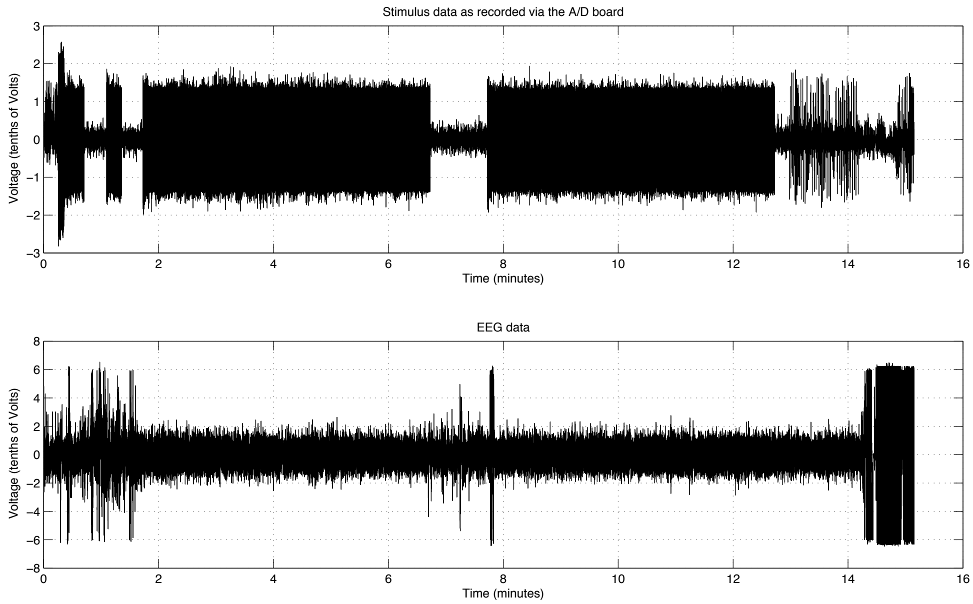

Figure 4.1. Data collected from an experimental session lasting about 15 minutes (stimulus and EEG). The top graph shows stimulus data, as acquired by the A/D board. The bottom graph shows EEG data. The signal is shown as-recorded, before the application of any signal pre-processing. The actual experiment begins slightly before the 2 minutes mark; by then, the subject was already wired but engaging in conversation until 30 seconds before the onset of the sounds belonging to the first experimental block. Around the 7-minute mark, there was a minute of silence, separating the two experimental blocks. Data is from Subject 1.

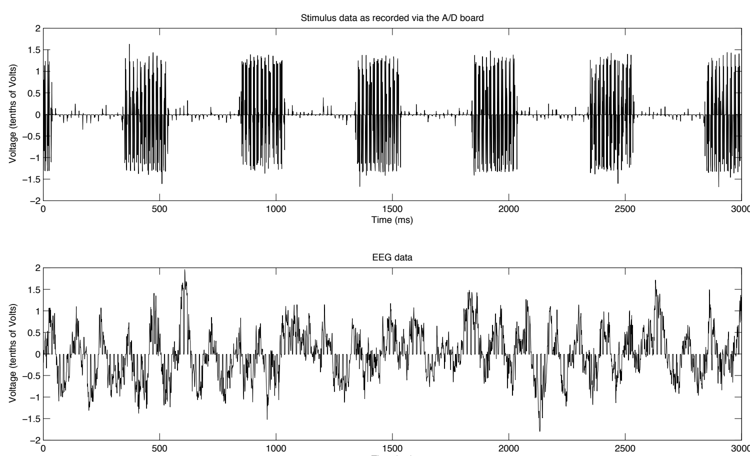

Figure 4.2. Zoom to 3 seconds of data shown in figure 4.1. Data is shown as-recorded, without the application of any signal pre-processing. The top and bottom graphs are synchronized. The top graph shows the acoustic stimuli as acquired by the A/D board, and the bottom graph shows the EEG signal recorded from Fz. Data is from subject 1.

4.2. SINGLE TRIALS

4.2.1. EXAMPLES OF SINGLE TRIAL DATA

Examples of one hundred consecutive single trials, after filtering, baseline correction, and epoch rejection, are shown in Figure 4.3. Trials are identified as standard or deviant.

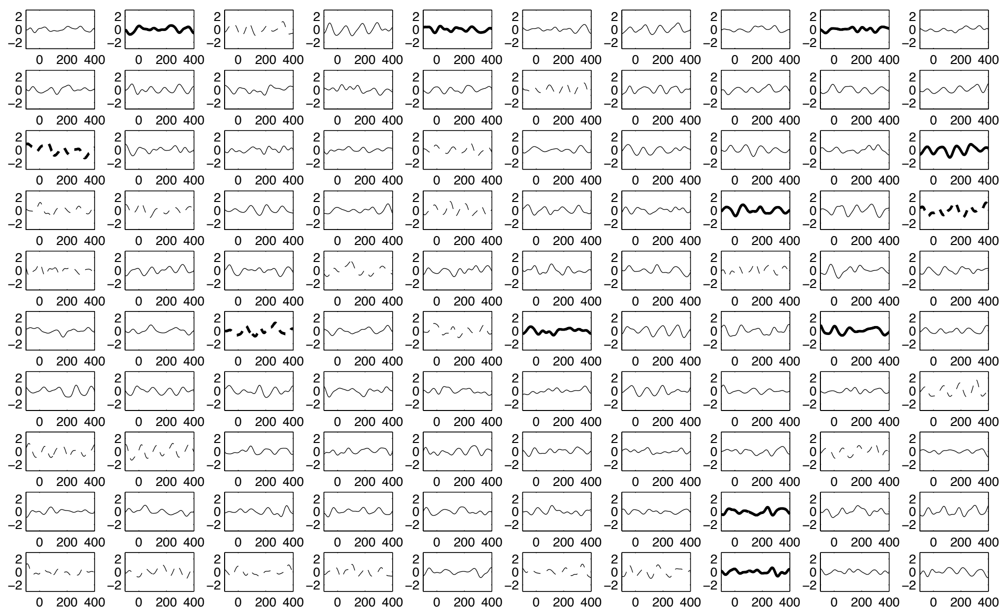

Figure 4.3. One-hundred consecutive single-trial recordings. Trials are sorted from top to bottom and from left to right. Rejected trials are drawn in broken lines. Deviant epochs are drawn in double-weight lines. Data have been subject to filtering and baseline correction, as described in the previous chapter. Data are from the 100 first epochs of block 2 of Subject 1.

4.2.2. RESULTS OF DATA REJECTION PROCEDURES

Data rejection is performed as described in the *Experimentation* chapter. The percentage of rejected epochs in each block is indicated on Table 4.1. Data from subjects 5, 6, and 7 were discarded, due to rejection of more than half the epochs. The number of remaining epochs of each type, for each subject and session is shown in Table 4.2. These are the epochs that will be used in the analysis that follows.

Subject, session[a]	% epochs rejected	
	Block #1	Block #2
Subject #1	14.67	10.17
Subject #2	11.17	9.50
Subject #3, session 1	21.50	15.83
Subject #3, session 2	15.83	7.00
Subject #4, session 1	27.17	32.67
Subject #4, session 2	32.67	39.50
Subject #5, session 1	55.33	59.00
Subject #5, session 2	59.00	61.17
Subject #6	58.33	11.50
Subject #7	75.50	70.00
Balloon[b], session 1	15.67	5.17

Table 4.1. Percentage of rejected epochs for each subject and session of experiments. Epoch rejection is performed automatically as described in the *Methods* section. If more than half the trials in a session are discarded, the data for the whole session is left out. As such, 3 subjects, namely, 5, 6, and 7, spanning 4 rounds, were eliminated from further analysis. a. For subjects for which 2 sessions were run, the second block of the first round is the same as the first block of the second session, thus the equivalency in numerical values for percentage of rejected trials. b. All procedures for data collection and analysis were repeated on a balloon, to validate the experimental setup against various possibilities for data contamination.

Subject, session	S_L	D_H	S_H	D_L
1	430	71	399	71
2	450	76	416	72
3,1	428	74	371	64
3,2	432	74	470	82
4,1	311	52	365	60
4,2	332	51	316	55

Table 4.2. Number of epochs of each type remaining after epoch rejection. S_L: standard low tone; D_H: deviant high tone; S_H: standard high tone; D_L: deviant low tone.

4.3. Analysis of evoked potentials

4.3.1. Averaged waveforms

Plots of evoked potentials are shown in four figures. Figure 4.4 shows grand average curves for: 1. (tone, condition) pairs; 2. pMMN; 3. cMMN. Curves obtained in isolated rounds of experiments, in an intra-subject basis, are shown in figures that follow it: 4.5, 4.6 and 4.7. Tables of numerical values for peak amplitude and latency are provided for each of the figures.

Care should be exercised when looking at grand average curves (Figure 4.4), as there are important inter-subject variations (Figures 4.5, 4.6, 4.7). Grand average plots were included mostly so as to acknowledge the tradition in ERP research. One should look for possible differences among the members of the ppMMN (the goal of this thesis) at both the individual and the populational levels.

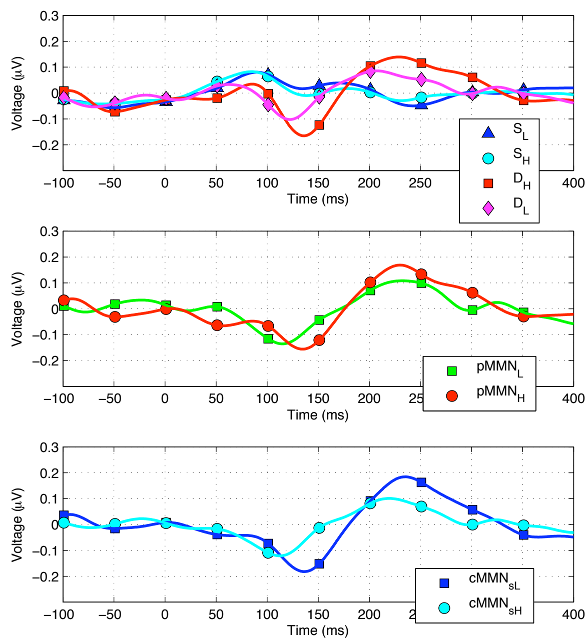

Figure 4.4. Grand-average waveforms. Tone onset is at the 0ms mark. Numbers for peak amplitudes and latencies are shown in Table 4.3.

ERP	Peak amplitude (μV)	Peak latency (ms)
D_H	-0.165	136
D_L	-0.102	122
$pMMN_L$	-0.136	115
$pMMN_H$	-0.156	135
$cMMN_{SL}$	-0.182	136
$cMMN_{SH}$	-0.121	112

Table 4.3. Amplitude and latencies for grand average waveforms shown in Figure 5.4. No peak in the MMN latency range can be identified for standard tones. $pMMN_L$ and $cMMN_{SH}$ are calculated using D_L and their latencies are in the [112, 115] ms interval; $pMMN_H$, and $cMMN_{SL}$ are calculated using D_H, and their latencies are in the [135,136] ms interval.

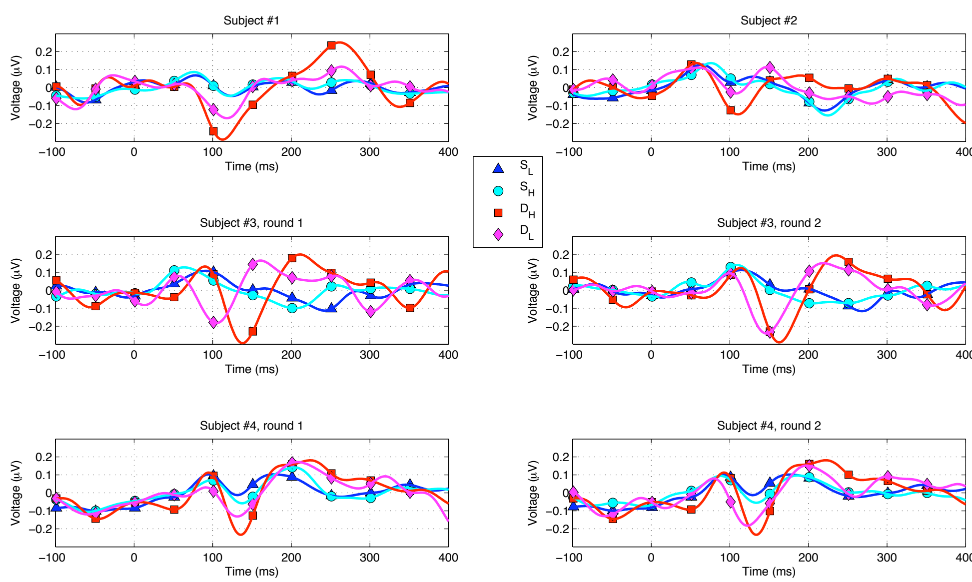

Figure 4.5. ERP's for each (tone, condition). Potentials for each (tone, condition) are presented, as average curves for each subject in each round of experiments. One round of experiments consists in the presentation of two blocks of stimuli, in which roles of tones as standard or deviant are reversed. The tones utilized are 196.0 and 466.2 Hz, each added of their first two harmonics. Rounds numbered "1" or left unmarked have the lower tone presented as standard in the first block; rounds numbered "2" have the higher tone presented as standard in the first block. Tone onset is at the 0ms mark. Probability of deviant is 15% regardless of which of the two tones is used as deviant.

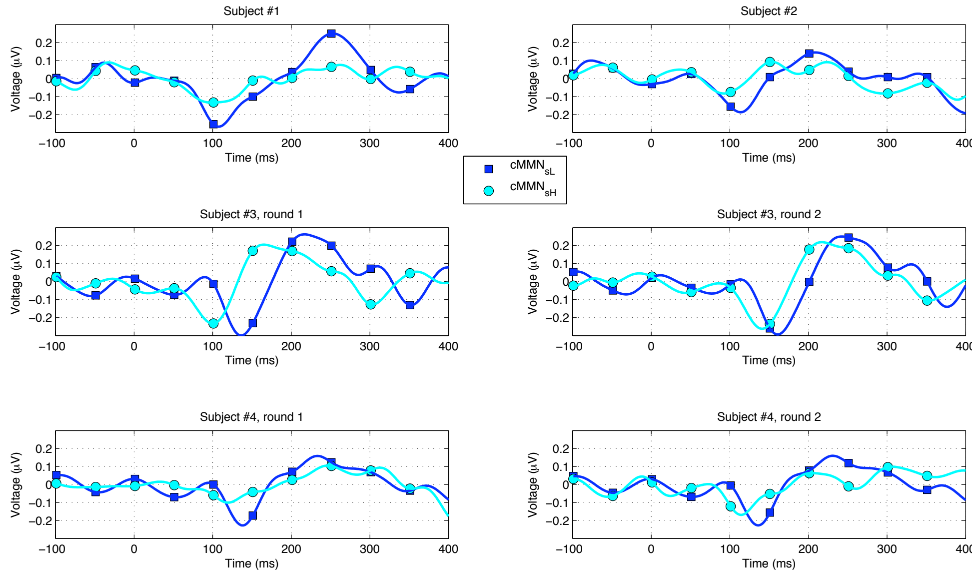

Figure 4.6. cMMN: cMMN plots are shown as subtraction of averaged curves, for each subject and round of experiments. cMMN's, or "classical" MMN's, are computed as the subtraction of the ERP for the standard from the ERP for the deviant. Standard and deviant stimuli are presented in random alternation, in the same block, and consist of physically different stimuli. This is how MMN is traditionally computed in the literature. The fact that the two curves presented in each graph are not the same is not enough to conclude that the MMN is a distortion metric, as physical characteristics of the stimuli are different and other ERP components which may vary according to these characteristics could be lurking within the curves. Because of the presence of this sort of non-MMN ERP components in the MMN curve, it is advisable to compute the MMN as what we call the "pure" MMN, shown in Figure 5.7. Tone onset is at the 0ms mark. Values for peak amplitudes and latencies are shown in Table 5.4.

Subject, round	Amplitude of cMMN peak (μV)		Latency of cMMN peak (ms)	
	cMMN$_{sL}$	cMMN$_{sH}$	cMMN$_{sL}$	cMMN$_{sH}$
1, 1	-0.267	-0.133	108	99
2, 1	-0.187	-0.083	114	92
3, 1	-0.300	-0.233	136	100
3, 2	-0.294	-0.262	161	141
4, 1	-0.227	-0.100	138	119
4, 2	-0.227	-0.168	136	114

Table 4.4. Comparison of latencies and amplitudes of cMMN$_{sL}$ and cMMN$_{sH}$ peak amplitudes and latencies, in the per-(subject, round) average waveforms.

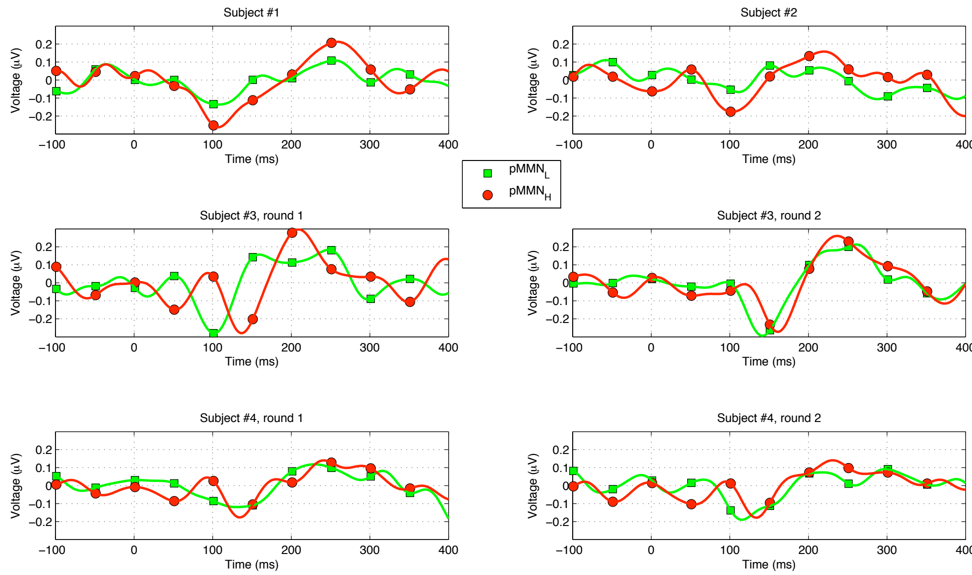

Figure 4.7. pMMN. pMMN's are shown as subtraction of averaged curves, for each subject and round of experiments. pMMN's, or "pure" MMN's, are computed as the subtraction of the ERP for the standard from the ERP for the deviant, but, as opposed to how it's traditionally done in the cMMN, standard and deviant consist of physically identical stimuli. This is achieved by computing pMMN's from two blocks of experiments, in which probability of deviant is kept constant, but roles of standard and deviant for each of the two different physical stimuli used are exchanged. pMMN is the subtraction of the ERP for tone x presented as standard against tone y from the ERP of tone x presented as deviant against tone y. By doing this, the effects of non-MMN ERP components are completely cleared up, except of course for noise effects. If the cMMN were a distance metric, the curves for the two pMMN's thus obtained would be the same; according to the experimental results hereby shown this is not the case and the MMN is a distortion metric. Tone onset is at the 0ms mark. Values for peak amplitudes and latencies are shown in Table 4.5.

Subject, round	Amplitude of pMMN peak (μV)		Latency of pMMN peak (ms)	
	$pMMN_L$	$pMMN_H$	$pMMN_L$	$pMMN_H$
1, 1	-0.136	-0.262	108	107
2, 1	-0.067	-0.177	111	103
3, 1	-0.281	-0.280	102	137
3, 2	-0.294	-0.273	141	161
4, 1	-0.119	-0.177	130	134
4, 2	-0.190	-0.178	115	134

Table 4.5. Comparison of latencies and amplitudes of $pMMN_L$ and $pMMN_H$ peak amplitudes and latencies, in the per-(subject, round) average waveforms.

4.3.2. MMN’S UNDER SAMPLE ANALYSIS

Statistical significance tests comparing epochs for standard and deviant, along with measures of effect sizes, are given in Tables 4.6 and 4.7, for comparisons defined, respectively, by cMMN (standard low x deviant high and standard high x deviant low) and pMMN (standard low x deviant low and standard high x deviant high).

The statistical significance tests were run according to the methodology described in (Näätänen et al., 2004), and, additionally, effect size measures were taken. Peak latency for every sample is given by the peak latency in the average MMN curve calculated for each (subject, round). These latency values are listed in tables 4.4 and 4.5, respectively, for cMMN and pMMN. Epoch amplitude is given by the average amplitude in the 7 ms interval around the peak latency. Sample peak amplitudes are compared by a paired t-test and by the effect size measure *Cohen’s d,* or *d’*, which measures the difference between the sample means in units of pooled standard deviations, as explained in the glossary (Cohen 1988).

Subject, round	**S_L x D_H**		**S_H x D_L**	
	d’	**P**	**d’**	**p**
1	0.43	0.0003	0.36	0.0041
2	0.28	0.0229	0.15	0.2268
3, 1	1.03	0.0000	0.54	0.0000
3, 2	0.40	0.0014	0.33	0.0056
4, 1	0.83	0.0000	0.33	0.0141
4, 2	0.83	0.0000	0.58	0.0001
Mean, standard deviation	(0.63, 0.3)		(0.38,0.16)	

Table 4.6. p-values and d’ for cMMN peak amplitudes. Amplitude was calculated as the average amplitude in the 6ms interval centered around the peak of the cMMN average waveform for each (subject, round). Sample analysis point to detection of significant (α = 3%) cMMN for all Subjects and experimental blocks except for Subject number 2, blocks of type S_H x D_L. A positive value for d’ indicates that the first term in the comparison has higher sample mean than the second term.

Subject, round	S_L x D_L		S_H x D_H	
	d’	p	d’	p
1	0.38	0.0029	0.45	0.0002
2	0.21	0.0854	0.22	0.0692
3, 1	0.73	0.0000	0.82	0.0000
3, 2	0.34	0.0054	0.28	0.0225
4, 1	0.42	0.0019	0.67	0.0000
4, 2	0.75	0.0000	0.61	0.0000
Mean, standard deviation	(0.47, 0.22)		(0.51, 0.23)	

Table 4.7. p-values and d’ for pMMN. Amplitude was calculated as the average amplitude in the 7ms interval centered in the peak of the pMMN average waveform for each (subject, round). Sample analysis point to detection of significant (α = 2.25%) pMMN for all Subjects but number 2 in all experimental blocks. At α = 9% the results for Subject number 2 become significant. A positive value for d’ indicates that the first term in the comparison has higher sample mean than the second term.

Tables 4.6 and 4.7 show, through the paired t-test, that there are significant statistical differences between the amplitudes of samples of standard and deviant, and this means there is an MMN. An effect size measure is given for the MMN amplitude.

But the values of p and d’ shown in Tables 4.6 and 4.7 do not really give an answer to the question of whether the MMN, given the choice of M_φ, is a distance or distortion metric – though the difference between the effect size measures for amplitudes of $pMMN_L$ and $pMMN_H$ is an evidence.

In Table 4.8, the preceding methodology is adapted by including a re-sample step, in which subsets of N samples of deviants and N samples of standards are randomly chosen from the pool of ERP's. An MMN is computed from those 2N samples. As before, peak amplitude is the average amplitude in the 7 ms interval around the peak latency. The sample amplitudes determine a d'. From each re-sample step, three values are derived: peak latency and amplitude, from the averaged curve, and d' for within-resample sample amplitude comparison (i.e., a comparison of samples of 45 ERP's of deviants and 45 ERP's of standards). The re-sampling process is repeated M times. Results for N = 45 and M = 600[13] are shown in Table 4.8.

Subject, round	**d' ($pMMN_L$ x $pMMN_H$)**			**p-value**		
	Latency	Amplitude	d' (standard x deviant)	Latency	Amplitude	d' (standard x deviant)
Subject 1	-0.14	-0.31	0.28	1.4e-2	6.2e-8	1.3e-6
Subject 2	-0.29	-0.18	0.19	5.7e-7	1.5e-3	1.2e-3
Subject3, round 1	-0.08	-0.16	0.10	0.16	4.6e-3	8.3e-2
Subject 3, round 2	-0.04	-0.13	-0.04	0.54	2.2e-2	4.5e-1
Subject 4, round 1	-0.05	-0.11	0.14	0.42	5.3e-2	1.4e-2
Subject 4, round 2	-0.38	-0.21	0.24	8.7e-11	2.2e-4	4.7e-5

Table 4.8. Re-sample analysis of characteristics of $pMMN_L$ compared to those of $pMMN_H$. Random samples of N deviant ERP's and N standard ERP's are randomly chosen in each re-sample step. A pMMN curve is computed. Peak latency l_{rs} and amplitude a_{rs} are determined. A d-prime value is also computed, to compare deviant and standard amplitudes within the re-sample step. sample amplitude is calculated as the average amplitude in the 7ms interval centered around the peak of the pMMN average waveform determined by the re-sample step. Positive values for d' indicate that the first term in the comparison has higher sample mean than the second term. This table demonstrates a tendency towards larger amplitudes and larger latencies for $pMMN_H$.

[13] As a quick-and-dirty method for identifying the peak within the MMN latency range, re-sampling was done 1000 times with rejection of 20% latency outliers from each side. The process for peak identification is to choose the time of the minimum amplitude value within the pMMN latency range, taken as 90 – 175 ms. Elimination of outliers leaves a normal distribution of latencies, identified by a Lilliefors test (Lilliefors, 1967). If anything this process makes the samples more homogeneous.

CHAPTER 5. DISCUSSION

5.1. THE ANALYSIS OF EXPERIMENTAL DATA

It was interesting to note that the same bias toward higher peak latency and amplitude for $pMMN_H$ than for $pMMN_L$, initially suggested by the grand-average curve, was confirmed for every (subject, round) by the d' values of latency and amplitude in re-sampling analysis, shown in Table 4.8, even though this trend was not so clear in the mid-term analysis of (subject, round) average curves (Table 4.5) nor even in the comparison of d-primes for S_L x D_L with d-primes for S_H x D_H , which does not show a definite bias (Table 4.7).

Perhaps the re-sampling process presented here for the first time could be incorporated into ERP practice.

The validity of the p-values obtained by re-sampling is not clear: there is potential repetition of data, which can increase the sample size up to the number of all possible combinations C(number of standards, N) * C(number of deviants, N), where N is the number of ERP's of each type entering each re-sample step. But the samples are not exactly the same because the amplitude is determined by the latency of the average curve determined by all ERP's entering that particular re-sample. A more careful statistical analysis would be advised in order to correctly interpret the p-values thus obtained. Nevertheless, the effect size measures are reliable, and, in the case of the data collected for this experiment, have shown a clear bias toward higher latency and amplitude for the peak of $pMMN_H$ than for the peak of $pMMN_L$.

Lastly, revisiting once more point II. from (Näätänen 1990, 1992), presented in section 2.2, it's commonly assumed that larger peak latencies are associated with smaller peak amplitudes, and, conversely, smaller latencies are associated with larger amplitudes,

> The larger the difference between deviant and standard stimuli, the larger the MMN's amplitude, and the smaller its peak latency.

The reason why the opposite tendency, of both larger amplitude and longer latency for $pMMN_H$ than for $pMMN_L$, was observed in these experiments, is an open question.

5.2. Published results on the effect of deviance direction on the MMN

The literature considers the MMN to be a symmetrical measure of change. Against that assumption, one paper, published in 2009, by Colin et al., found an "unexpected" effect of deviance direction on the duration MMN. A sentence describing the surprisingness of their finding is quoted below:

> The data analysis reported here was performed in order to verify the serendipitous finding of an effect of deviance direction on the MMN parameters, an issue that has been hardly addressed in the literature.

The authors concluded it was a phenomenon "of pure electrophysiological nature", because it had no "psychophysical counterpart", and that it could be accounted for "in terms of degree of synchronization of MMN generating neurons". The first paragraph of their conclusion is quoted below:

> We found a major effect of deviance direction on MMN amplitude. Since it has no psychophysical counterpart, we propose that this phenomenon is of a purely electrophysiological nature and may be accounted for in terms of degree of synchronization of MMN generating neurons. For short deviants, deviance detection and quantification occur both at the same time, giving rise, whatever standard duration (within the values used in this study), to well-defined MMNs with latencies accurately indexing the moment of deviance detection. For long deviants, deviance quantification occurs later than deviance detection and this difference increases with standard durations. Consequently, MMN generating neurons are less and less well synchronized as standard durations increase, giving rise to poorer and poorer MMNs.

Which is an interesting explanation for the deviance direction effect on the duration MMN, and may be part of the explanation for the effect of deviance direction on the duration MMN. Or it may be the whole explanation.

To make sense of the assumption that the MMN is a symmetrical measure of change, section 5.4 presents a carefully constructed argument showing that such an idea, while on the surface being easy to understand, in fact lacks a good dose of formalism, and begs for extra assumptions.

5.3. Correctly interpreting pMMN's

The literature review hereby conducted on usage of the pMMN has found one single citation, in the review (Kujala et al., 2007), under the section *"Recent paradigm improvements"*, of straightforward pMMN usage, with no detailed description of the work done nor explicit citation of any article that used the pMMN. My own literature review could not find any such article either. Usage of the pMMN is advised for controlling for exogenous effects on the MMN, but caution is advised:

> However, the usage of physically identical stimuli serving in some blocks as deviants and in the other blocks as standards will not altogether abolish contributions of various refractoriness effects on the MMN. This is an issue for all sound dimensions that are processed by feature-specific neurons. A good example is frequency processing, which is based on tonotopic organization (...)

The assertion is that extraneous ERP's can lurk into the pMMN calculation due to refractoriness effects if the features being compared are processed by feature-specific neurons.

> (…) When, for example, the deviant stimulus has a low frequency and the standard a high frequency, the more frequent presentation of the standard stimulus will cause a larger degree of refractoriness in neuron specialized in the frequency of the standard. These neurons will show reduced activity and, as a consequence, the standard will yield smaller obligatory components such as P1 or N1.

No mention is made about the necessary proximity of higher and lower tones for this refractoriness effect to occur.

The assertion made in the citation can be examined in light of the experimental data gathered here. Looking at figures 4.4 and 4.5, one can see that the ERP's for standard low and standard high are coincident. What causes the difference in the pMMN curves obtained is not a difference in the curves for standards, as suggested by (Kujala et al., 2007), but a difference, clearly seen in the referred figures, between the ERP's for the deviants. The whole subsection from that review is reproduced in Box 5.1, in the next four pages:

Recent paradigm improvements

Controlling the exogenous effects on MMN

The traditional approach in recording the MMN has several problems. First, without appropriate control conditions, exogenous/obligatory responses differently contributing to the repetitive standard stimulus and the rare deviant stimulus affect the results. For example, when the MMN for deviations in sound duration has to be determined, the offset-N1 will be elicited at different latencies depending on the durations of the sounds. When the deviant is of shorter duration than the standard it will have the offset-N1 at a shorter latency than the standard which may erroneously be interpreted as MMN in the deviant–standard difference wave. Vice versa, when the deviant is longer than the standard, the MMN to the longer deviant may fall in the time range where the offset-N1 to the shorter standard is to be expected. Thus, when subtracting the ERP to the standard (containing the offset-N1) from the ERP to the deviant (containing the MMN), no MMN might be visible in the difference wave (although there is one). This problem arises with any sound including variation over time such as speech stimuli or environmental sounds.

An easy but time-consuming way to overcome this problem is to measure the deviant ERP and the standard ERP for physically identical stimuli. This can, for example, be achieved by reversing the role of standards and deviants between blocks, that is, the deviant becomes the standard and the standard the deviant in separate blocks. As a consequence, the physical differences will contribute equally to standard and deviant ERP’s. Another, less time-consuming, approach is to include one block in which only the stimulus that serves as deviant in the oddball blocks is presented. The respective ERP can then be used as the standard ERP.

However, the usage of physically identical stimuli serving in some blocks as deviants and in the other blocks as standards will not altogether abolish contributions of various refractoriness effects on the MMN. This is an issue for all sound dimensions that are processed by feature-specific neurons. A good example is frequency processing, which is based on tonotopic organization. The auditory system is organized in a tonotopic way from the cochlea to the cortex, so that different frequencies are mapped to (partly) different neurons (Pantev et al., 1988; Romani et al., 1982). **When, for example, the deviant stimulus has a low frequency and the standard a high frequency, the more frequent presentation of the standard stimulus will cause a larger degree of refractoriness in neurons specialized in the frequency of the standard. These neurons will show reduced activity and, as a consequence, the standard will yield smaller obligatory components such as P1 or N1.** When a deviant stimulus is presented, neurons that are sensitive to the features of the deviant come into play. Since they are less refractory than neurons processing the standard stimulus, the neurons specialized to the features of the deviant generate larger obligatory ERPs than neurons activated by the standard stimulus. **Especially the increase in N1 (and sometimes in N2) may be mistakenly interpreted to be a genuine MMN even though it actually is a joint N1 and MMN effect.**

By designing appropriate control conditions, one may avoid contributions from various refractoriness effects. In one such control condition (Fig. 3), the stimulus set includes several sound exemplars varying along the dimension characterizing the deviant. For example, when a 500 Hz tone serves as a deviant among 550 Hz standard tones in the oddball block (deviant probability being 10%), it will be presented in a control block using altogether 10 different stimuli with frequencies of 500, 550, 605, 666, 732, 805, 886, 974, 1072, and 1179 Hz. Therefore, neurons tuned to frequencies of about 500 Hz will not have a higher degree of refractoriness in the control condition than in the oddball condition since they are presented with the same probability as the physically identical tones serving as deviants in the oddball condition. This manipulation prevents the contribution of the relative increase of N1 elicited by deviant stimuli to the MMN; in fact, the ‘‘true’’ MMN measured with this controlled paradigm may even be underestimated (cf., e.g., Jacobsen and Schröger, 2001; Näätänen and Alho, 1997; Schröger and Wolff, 1996).

Variations of this paradigm controlling for refractoriness effects have been applied to frequency MMN (Jacobsen and Schröger, 2001), location MMN (Schröger and Wolff, 1996), intensity MMN (Jacobsen et al., 2003), and duration MMN (Jacobsen and Schröger, 2003). These studies showed that when using this paradigm for controlling the exogenous effects, a genuine MMN is present for each deviant type. However, it also turned out that this controlled paradigm yields a comparable, but not identical, MMN as the MMN obtained in the classical oddball condition. Thus, it is not always necessary to use this controlled protocol. Yet, whenever there is a large physical difference between the deviant and standard stimulus or when changes in temporal aspects of a stimulus are involved (e.g., duration), at least a simple control condition with a repetitive stimulus physically identical to the stimulus serving as the deviant in the oddball condition is recommended.

	Frequency [Hz]									
Condition	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
Oddball	500	550	550	550	550	550	550	550	550	550
Control	500	550	605	666	732	805	886	974	1072	1179

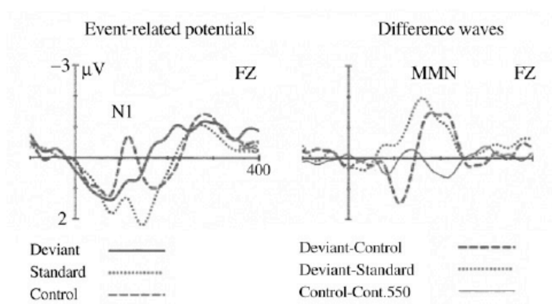

Fig. 3. Experimental protocol for controlling the refractory effects when recording MMNelicited by frequency changes. Top: The frequencies used in the oddball and control conditions are shown. In the oddball condition the frequency of the deviant is 500 Hz (S1) and that of the standard 550 Hz (S2–S10). In the control condition, the 500 Hz deviant stimulus is equiprobably presented with the other nine stimuli of different frequencies (S2–S10). The ‘‘classical’’MMN is measured in the oddball condition by subtracting the ERP elicited by the standard 550 Hz stimulus from the ERP elicited by the deviant 500 Hz stimulus. The MMN with no refractoriness effects can be obtained by subtracting the ERP to the 500 Hz stimulus (S1) obtained in the control condition from the ERP (S1) to the 500 Hz deviant stimulus obtained in the oddball condition. Bottom (left): The ERPs to the deviant (500 Hz) and standard (550 Hz) stimulus of the oddball condition and to the control (500 Hz) stimulus are shown; (right) the difference waves obtained in the oddball condition (dotted line) and those obtained by subtracting the ERP to the 500 Hz stimulus of the control condition from the 500 Hz deviant stimulus (oddball condition; dashed line) are shown. In addition, the difference wave resulting from a subtraction of the ERP to the 550 Hz stimulus from that to the 500 Hz stimulus in the control condition (continuous line) is shown. Figure adapted from Jacobsen and Schröger (2001).

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Box 5.1. Text reproduced from (Kujala et al., 2007).

5.4. A NOVEL, MORE RIGOROUS FORMALIZATION OF THE PROPERTIES OF THE MISMATCH NEGATIVITY

This section presents an analysis of fundamental mathematical properties of metric spaces in the domain of physical stimuli and in the domain of MMN waveform. Based solely on mathematical principles, a new paradigm for MMN experiments is suggested, and light is shed upon prematurely derived experimental conclusions from the literature.

5.4.1. RIGOROUSLY DEFINING THE ASSUMPTION OF SYMMETRY OF THE MMN WAVEFORM TO DEVIANCE DIRECTION

The defining properties of the MMN waveform, given in Näätänen (1990, 1992), were stated in the chapter 2, and are repeated here for recapitulation:

I. The smaller the probability of occurrence of the deviant within the sound sequence, the larger the MMN's amplitude.
II. The larger the difference between deviant and standard stimuli, the larger the MMN's amplitude, and the smaller its peak latency.
III. The MMN is elicited whether the subjects are instructed to detect the deviant sounds or are engaged in a neutral primary task (e.g., reading a book). In the first case, though, the waveform is overlapped by attention- and task-dependent components, such as the P165 and the N2b (see, e.g., Sams, Paavilainen, Alho, & Näätänen, 1985).

Point II listed above uses the expression “difference between deviant and standard stimuli” – it is an apparently straightforward verbal construct, but collapses into ambiguity under the pressure of mathematical rigour: in how many different ways can one measure *difference* between two stimuli? Which metrics in the physical domain ϕ will have an easy correspondence in the psychological domain ψ? Copernicus’ heliocentric model of elliptic planetary orbits is more clear in ψ-world than the geocentric models (though one is as good as the other in the ϕ-world, actually, there are no “models” in the ϕ-world). In ψ, it’s “easier” to work with ellipses than with “irregular” trajectories. Just as well, using a ratios scale for frequency seems to be more natural than using a subtractions scale: in a piano, going from the set of keys representing one “octave” to the set of keys representing the next “octave”, the frequency of each note is doubled. Back to the MMN, if the MMN metric space is easily mapped into the ψ metric space, then finding a simple mapping from ϕ-space to MMN-space will help understand how ϕ is mapped into ψ.

Take notice that Point II from Näätänen (1990,1992) is currently still widely accepted in the research community, as clearly stated in the most canonical recent review on the MMN (Näätänen, Paavilainen, Rinne & Alho, 2007):

> In general, the MMN amplitude gets larger and peak latency shorter with the increasing magnitude of stimulus deviation.

And so the aforementioned review continues, opportunely to the argumentation based on the frequency MMN to be exposed in the remaining of this chapter:

> For the frequency change of a sinusoidal tone, this was shown by several studies [e.g., Sams et al., 1985a; Lang et al., 1990; Tiitinen et al., 1994; Berti et al., 2004; Näätänen et al., 1997; Yago et al., 2001a,b; Novitski et al., 2004, 2007[14]].

Let's now try to define a few sensible metrics for the ϕ-space of sinusoidal tones of same amplitude. Let X and Y be sinusoidal tones, with measures x and y, in Hertz. One can initially think of:

$$M_{\phi}^{1}(X,Y) = |x - y|$$

$$M_{\phi}^{2}(X,Y) = |y - x| / x$$

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[14] Sams M, Paavilainen P, Alho K, Näätänen R. Auditory frequency discrimination and event-related potentials. Electroencephalogr Clin Neurophysiol 1985a;62:437–48.

Lang HA, Nyrke T, Ek M, Aaltonen O, Raimo I, Näätänen R. Pitch discrimination performance and auditory event-related potentials. In: Brunia CHM, Gaillard AWK, Kok A, Mulder G, Verbaten MN, editors. Psychophysiological brain research 1990; vol. 1. Tilburg, the Netherlands: Tilburg University Press; 1990. p. 294–8.

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which are, respectively, the absolute value of the difference in Hertz between the two tones, and the relative change from one tone to the other.

The first of them is a *distance* metric, the second of them is a *distortion* metric. Distance metrics display symmetry:

$$\forall(x,y): d(x,y) = d(y,x)$$

but distortion metrics do not.

It's also interesting to apply, to ϕ, mathematical transformations that are ψ-inspired, like the Mel frequency scale (Stevens, Volkman, & Newman, 1937), illustrated in Figure 3.1.

$$M_{\phi}^{3}(X,Y) = M_{\phi}^{1}\big(mel(X), mel(Y)\big)$$

$$\text{where } mel(X) = 2595\log_{10}\left(X/700 + 1\right) = 1127\log_{e}\left(X/700 + 1\right)$$

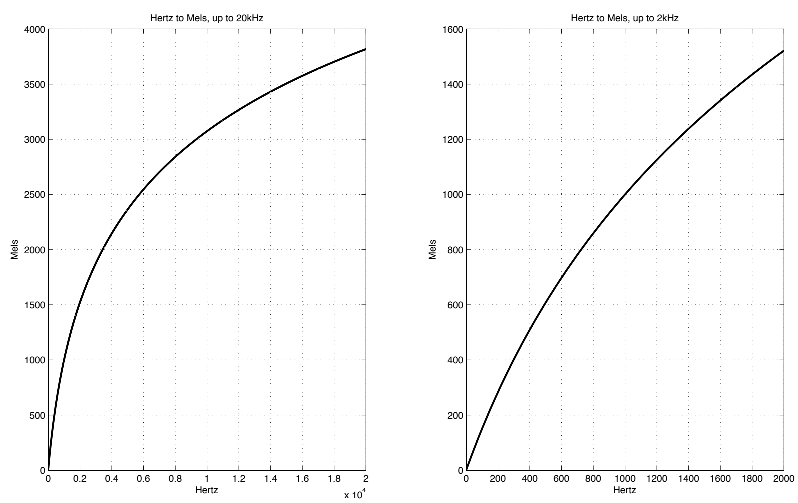

Figure 5.1. Mel frequency scale. The figure on the left shows the Hertz-to-Mels relationships up to 20kHz, the upper frequency limit of human hearing; the figure on the right is zoomed in for the first 2kHz. By definition, 1kHz = 1kMel. The Mel frequency scale aims at relating psychological pitch to frequency in Hertz. It has been constructed on the basis of experimental procedures so that equal steps in Mels are equal in subjective size. Two experimental procedures were utilized: in the first one, subjects would hear a tone and be asked to set a variable tone to a pitch half as high. In the second procedure subjects would be asked to divide an interval into equal halves. A third, slightly more complicated procedure which will not be described here was applied to correct for the implicit presence of the concept of "zero pitch" in the second procedure, and results were equivalent. (Stevens, Volkman, and Newman, 1937, 1940). The term Mel refers to melody: the tones were heard in sequence and not as a chord.

5.4.2. A RECENT PARADIGM IMPROVEMENT FOR CALCULATING THE MMN, REVISITED: AN EXPERIMENTAL PARADIGM FOR MEASURING THE PMMN UNDER DISTORTION METRICS IN ϕ

The reader who chose to skip Chapter 2 is at this point asked to read section 2.2.1.

Let's call the MMN obtained according to the paradigm described in section 2.2.1 a "pure MMN" (pMMN). The two blocks of experiments, in which physical stimuli ϕ and ϕ' alternate their roles of standard and deviant, will define two pMMN's, one for subtraction of the ERP for ϕ-as-standard from ϕ-as-deviant, and another for subtraction of ϕ'-as-standard from ϕ'-as-deviant. They will be called, respectively, $pMMN_{\phi}$ and $pMMN_{\phi'}$. To distinguish the classical MMN from the pMMN, let's name the first cMMN from now on; more specifically, let's name it $cMMN_{standard,deviant}$, or, in cases where the deviant stimulus can be known from context, indicate only what is the standard stimulus, prefixed by the letter s, for example, $cMMN_{s\phi}$.

Now, suppose one wants to compare $pMMN_{\phi}$ to $pMMN_{\phi'}$. What would be the correct way of calculating the pair of pMMN's, from now on referred to as ppMMN? A ppMMN is hereby defined as a set of two pMMN's for which the numerical value of the metric function from standard to deviant is the same, as is the deviant probability.

It turns out that the correct experimental paradigm depends on whether one is considering a distance or a distortion metric in ϕ. In case of a distance metric, pMMN pairs (ppMMN) are calculated as described in Kujala (2007), but in case of distortion metrics, three blocks of experiments are needed. An example calculation of a ppMMN with metric M_{ϕ}^{2} is worked out in Box 5.2.

Let V, X, Y, and Z be pure tones with frequencies v, x, y, and z Hertz, respectively, satisfying the relationships below, with $k \in \Re$

$x = kv$

$y = kx$

$z = ky$

Then 3 blocks of experiments would be necessary to compute the ppMMN for X and Y, namely:

vS, xD (block I)

xS, yD (block II)

yS, zD (block III)

Compare xD from block I to xS from block II to get $pMMN_x$, and yD from block II to yS from block III to get $pMMN_y$.

$pMMN_x = xD – xS$

$pMMN_y = yD – yS$

Box 5.2. How to calculate a ppMMN when using a distortion metric in ϕ. When adopting a distance metric in ϕ, the procedure described in (Kujala, 2007) is appropriate for computing a ppMMN for stimuli ϕ_1 and ϕ_2: one simply needs to swap standard and deviant roles in a second block of the oddball paradigm, and subtract ϕ_i as standard from ϕ_i as deviant. When adopting a distortion metric in ϕ, though, one needs two extra stimuli and one extra block of the oddball paradigm, so that the distortion from deviant to standard is the same in all blocks, and ϕ_1 and ϕ_2 can each be presented as standard once and as deviant once, in two distinct blocks (only once they will belong in the same experimental block).

What about the MMN itself? Is it a distance or a distortion metric? Logically, if it's assumed that the cMMN is a distance metric, then it must also be assumed that the pMMN is a distance metric, furthermore, less contaminated by other ERP's than the cMMN. But the question of whether the MMN is a distance or distortion metric is not well-defined without choice of the metric space in ϕ, as not only the stimuli but also as the appropriate experimental paradigm for recording a ppMMN depend on whether that metric in ϕ is a distance or a distortion.

5.4.3. Conclusions about the effect of deviance direction on the MMN waveform

It is clear that whether the MMN is a distance or a distortion metric depends on what type of topology is chosen for the space of physical stimuli, ϕ.

If one postulates that the MMN is a distance metric, though, it becomes an interesting problem to figure out under what topologies of ϕ the MMN will actually behave as such.

5.5. Further experiments in psychophysics of tone frequencies

Shephard (1983) has shown the existence of at least three dimensions of perception of complex tones: a rectilinear dimension, and two circular dimensions, of chroma and of musical fifths, thus making the helicoidal structure of tone perception.

More recently, Kadosh et al. (2008) have related tone frequency perception to general numerical cognition. In that article, through reaction-time experiments in comparison of tones, they show a clear linear relationship between tone distance in semitones to subjective perception, that is, a logarithmic relationship between tone distance in Hertz and subjective perception, corroborating the Mel scale and the choice of a distortion function as the most ψ-appropriate one in the space of frequencies in Hertz.

CHAPTER 6. CONCLUSIONS

This chapter is divided in three subsections. Section 6.1 presents a brief summary of the series of experimental results that, under the choice of a specific metric for ϕ, the space of physical stimuli, lead to the definition of the MMN as a distortion metric. Section 6.2 revisits the current literature in search of explanations for the phenomena observed, and, in light of the data obtained in this work, suggests that the N100 explanation for possible differences in observed pMMN's is wrong. Finally, section 6.3 revisits section 5.4 and concludes that postulating the MMN as a distance metric provides an experimental framework for searching for psychotopologies relating to any stimuli for which the MMN provides a measure of discriminable change.

6.1. CONCLUSIONS FROM EXPERIMENTAL RESULTS

The absence of artifactual contamination of data was shown in the Balloon experiments, described in the Appendix, section A.2.

Tables 4.6 and 4.7 show that the experiments correctly measured the MMN: the p-values determined by comparison of standard and deviant ERP amplitudes are significantly (α = 3%) low. Comparisons required by both the cMMN or the pMMN yielded such result.

In Table 4.8, it was shown that, under the distance function chosen for ϕ:

$$M(\phi_1, \phi_2) = |\phi_1 - \phi_2|,$$

where ϕ_1 and ϕ_2 are the fundamental frequencies (in Hertz) of a three-harmonic complex tone,

the MMN is a distortion metric, with $pMMN_H$ peaking at longer latency and higher amplitude than $pMMN_L$. This is in agreement with what was initially suggested by the grand-average curve, plotted in Figure 4.4, with peak amplitude and latency quantified in Table 4.3.

6.2. CONCLUSIONS ABOUT EXPLANATIONS AVAILABLE IN THE LITERATURE FOR DIFFERENCES IN FREQUENCY PMMN'S

As discussed in section 5.3, the literature (Kujala, 2007) may be wrong about the supposed contamination of the pMMN by supposed refractoriness effects that would cause the standard tones to have smaller N100's when the deviant has a higher frequency than the standard. Data from Figures 4.4 and 4.5 suggest that the differences in the pMMN's are due to differences in the waveforms for the deviants. Perhaps the assertion from (Kujala et al., 2007) holds for frequencies that are closer by, but it cannot be generalized.

6.3. CONCLUSIONS FROM THEORETICAL DEVELOPMENTS

As discussed in section 5.4, whether the MMN is a distance or a distortion metric is a question that can only be answered conditioned on a choice for the metric $M(\phi_1, \phi_2)$ for ϕ, the space of physical stimuli.

It was shown that the choice of M also determines differences in the experimental paradigm for gathering the data from which to compute the ppMMN: in the oddball paradigm, two experimental blocks are needed for distance metrics, and three experimental blocks are needed for distortion metrics.

If one postulates that the MMN is in its essence a distance metric, then trying to find a metric in ϕ under which it behaves as such is an interesting problem that can help mapping the psychotopology of any sort of stimuli for which the MMN acts as a measure of discriminable change.

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APPENDIX. VALIDATION OF EXPERIMENTAL ENVIRONMENT

A.1. VALIDATION OF TIMING OF STIMULUS DELIVERY

The timing of stimulus delivery was measured and shown to be accurate. The .wav files were played, sampled by the NI acquisition board at 10kHz, and recorded without any filtering by LabView Signal Express, producing .csv files which were analysed by the Matlab script listed in Box A.1. Histograms of epoch length, as calculated by the script listed, are shown in figure A.1. The maximum variation in measured stimulus onset asynchrony (SOA) was 30 samples, which, at a sampling frequency of 10kHz, corresponds to 3ms. Such measured variation may have occurred due actual variations in timing of stimulus delivery or to errors related to the measuring process itself. Possible error sources are the method for calculating epoch length, noise in the signal acquisition process by the A/D board, or OS timing fluctuations.

It's worthwhile noting that playing the .wav files through an mp3 player (Sansa brand) introduced significant timing errors; this method of stimulus delivery is not recommended.

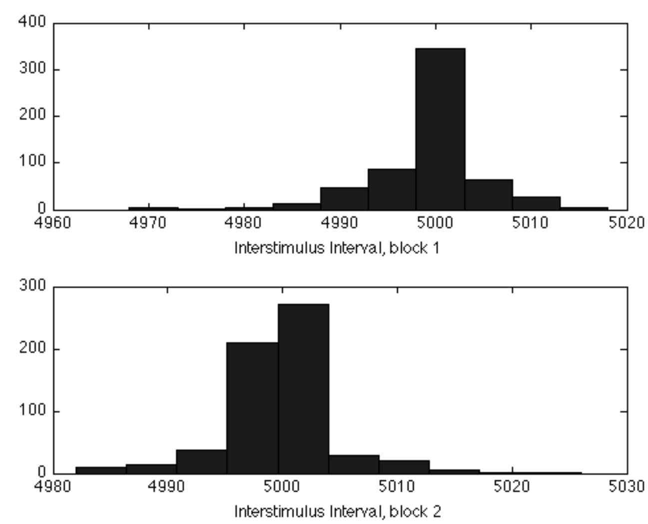

Figure A.1. Validation of timing of stimulus Delivery. Histograms show stimulus onset asynchrony (SOA) measured in number of samples, at a sampling rate of 10khz. The correct SOA is 500ms. The infrequent and small errors, which were considered to be acceptable in the context of these experiments, could be due to actual errors in delivery time, to errors in the calculation of SOA by the script listed in Box A.1, or to errors in the signal acquisition phase.

```
% interval in which there is no stimulus
% frequencies that are prominent in this interval will be filtered out:
p0=3.15e6;p1=3.45e6;

% 10kHz, sampling rate of the acquisition board.
fs=1e4;

% 8th order Butterworth band-pass filter for the frequency band [1kHz…3kHz]
% this choice is based on observation of the psd of the silent interval
[b,a]=butter(8,[1000/fs 3000/fs]);
z=filtfilt(b,a,block1);

%moving average parameter
MAP = 100;

y1=smooth(abs(z), MAP);
y2=y1>0.05; % y2 is 1 when there’s sound and 0 otherwise
y3=diff(y2);% 1 marks onset and -1 marks offset of sound
y4=find(y3==1); % indices of moments of onset
y5=diff(y4); intervals between onsets

figure; subplot(2,1,1);
hist(y5);
```

Box A.1. Matlab script for measuring inter-stimulus interval.

A.2. The Balloon experiments

As described in the *Methods* section, all procedures for data collection and analysis were repeated on a balloon, to validate the experimental setup against various possibilities for data contamination. Plots akin to those shown in Figures 5.5 – 5.7 are shown for the Balloon, in Figures A.2 – A.4.

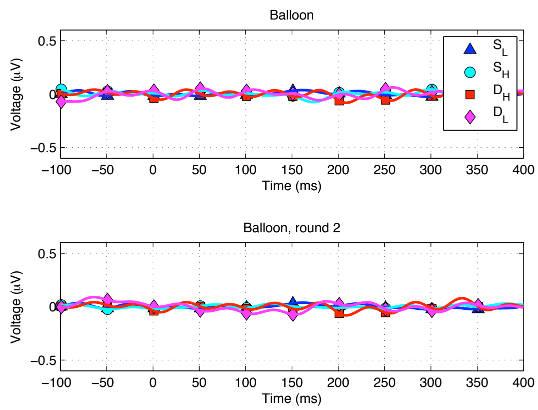

Figure A.2. ERP-like plots for each (tone, condition). Akin to Figure 5.5, but data comes from an air-filled balloon.

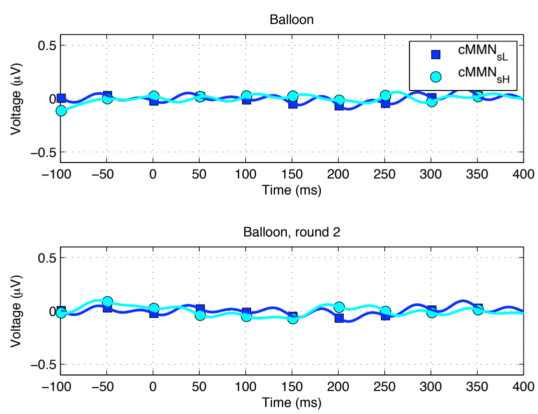

Figure A.3. cMMN-like plots. Akin to Figure 5.6, but data comes from a Balloon.

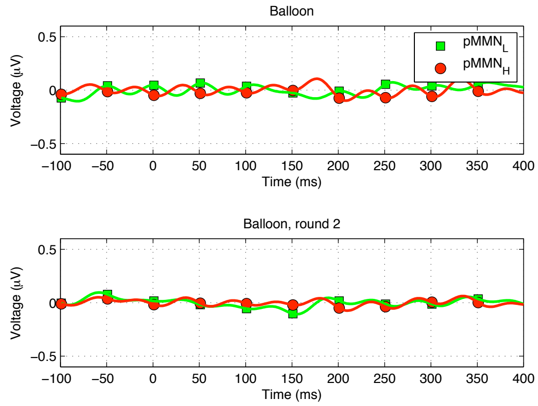

Figure A.4. pMMN-like plots. Akin to Figure 5.7, but data comes from a Balloon.

Theorem: There was no artifactual data contamination, Q.E.D.

Corollary: Ballons have no auditory evoked potentials, at least to the stimuli employed in these experiments.